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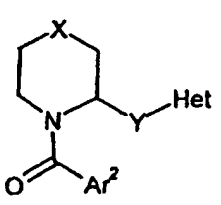
(54) Title: N-AROYL CYCLIC AMINE DERIVATIVES AS OREXIN RECEPTOR ANTAGONISTS



(I)

(57) Abstract: This invention relates to N-aroyl cyclic amine derivatives of formula (I), wherein X represents a bond, oxygen , NR^3 or a group (CH_2), wherein n represents 1, 2 or 3; Y represents CH_2, CO, CH(OH), or $CH_2CH(OH)$; Het is an optionally substituted bicyclic heteroaryl group containing up to 4 heteroatoms selected from N, O and S; Ar^2 represents an optionally substituted phenyl or a 5- or 6-membered heterocyclyl group containing up to 3 heteroatoms selected from N, O and S and their use as pharmaceuticals, specifically as orexin receptor antagonists.

N-AROYL CYCLIC AMINE DERIVATIVES AS OREXIN RECEPTOR ANTAGONISTS

This invention relates to *N*-aroyl cyclic amine derivatives and their use as pharmaceuticals.

Many medically significant biological processes are mediated by proteins participating in signal transduction pathways that involve G-proteins and/or second messengers.

Polypeptides and polynucleotides encoding the human 7-transmembrane G-protein coupled neuropeptide receptor, orexin-1 (HFGAN72), have been identified and are disclosed in EP-A-875565, EP-A-875566 and WO 96/34877. Polypeptides and polynucleotides encoding a second human orexin receptor, orexin-2 (HFGANP), have been identified and are disclosed in EP-A-893498.

Polypeptides and polynucleotides encoding polypeptides which are ligands for the orexin-1 receptor, e.g. orexin-A (Lig72A) are disclosed in EP-A-849361.

Orexin receptors are found in the mammalian host and may be responsible for many biological functions, including pathologies including, but not limited to, depression; anxiety; addictions; obsessive compulsive disorder; affective neurosis/disorder; depressive neurosis/disorder; anxiety neurosis; dysthymic disorder; behaviour disorder; mood disorder; sexual dysfunction; psychosexual dysfunction; sex disorder; sexual disorder; schizophrenia; manic depression; delerium; dementia; severe mental retardation and dyskinesias such as Huntington's disease and Gilles de la Tourett's syndrome; disturbed biological and circadian rhythms; feeding disorders, such as anorexia, bulimia, cachexia, and obesity; diabetes; appetite/taste disorders; vomiting/nausea; asthma; cancer; Parkinson's disease; Cushing's syndrome / disease; basophil adenoma; prolactinoma; hyperprolactinemia; hypopituitarism; hypophysis tumor / adenoma; hypothalamic diseases; Froehlich's syndrome; adrenohypophysis disease; hypophysis disease; hypophysis tumor / adenoma; pituitary growth hormone; adrenohypophysis hypofunction; adrenohypophysis hyperfunction; hypothalamic hypogonadism; Kallman's syndrome (anosmia, hyposmia); functional or psychogenic amenorrhea; hypopituitarism; hypothalamic hypothyroidism; hypothalamic-adrenal dysfunction; idiopathic hyperprolactinemia; hypothalamic disorders of growth hormone deficiency; idiopathic growth hormone deficiency; dwarfism; gigantism; acromegaly; and sleep disturbances associated with such diseases as neurological disorders, neuropathic pain and restless leg syndrome, heart and lung diseases; acute and congestive heart failure; hypotension; hypertension; urinary retention; osteoporosis; angina pectoris; myocardial infarction; ischaemic or haemorrhagic stroke; subarachnoid haemorrhage; head injury such as sub-arachnoid haemorrhage associated with traumatic head injury; ulcers; allergies; benign prostatic hypertrophy; chronic renal failure; renal disease; impaired glucose tolerance; migraine; hyperalgesia; pain; enhanced or exaggerated sensitivity to pain, such as hyperalgesia, causalgia and allodynia; acute pain; burn pain; atypical facial pain; neuropathic pain; back pain; complex regional pain syndromes I and II; arthritic pain; sports injury pain; pain related to infection, e.g. HIV, post-polio syndrome, and post-herpetic neuralgia; phantom limb pain; labour pain; cancer pain; post-chemotherapy pain; post-stroke pain; post-operative pain; neuralgia; nausea, vomiting; conditions associated with visceral pain including irritable bowel syndrome, migraine and angina; urinary bladder incontinence e.g. urge incontinence; tolerance to narcotics or withdrawal from narcotics; sleep disorders; sleep apnea; narcolepsy; insomnia; parasomnia; jet-lag syndrome; and neurodegenerative disorders, which

includes nosological entities such as disinhibition-dementia-parkinsonism-amyotrophy complex; pallido-ponto-nigral degeneration, epilepsy, and seizure disorders.

Experiments have shown that central administration of the ligand orexin-A (described in more detail below) stimulated food intake in freely-feeding rats during a 4 hour time period. This increase was approximately four-fold over control rats receiving vehicle. These data suggest that orexin-A may be an endogenous regulator of appetite. Therefore, antagonists of its receptor may be useful in the treatment of obesity and diabetes, see *Cell*, 1998, **92**, 573-585.

There is a significant incidence of obesity in westernised societies. According to WHO definitions a mean of 35% of subjects in 39 studies were overweight and a further 22% clinically obese. It has been estimated that 5.7% of all healthcare costs in the USA are a consequence of obesity. About 85% of Type 2 diabetics are obese, and diet and exercise are of value in all diabetics. The incidence of diagnosed diabetes in westernised countries is typically 5% and there are estimated to be an equal number undiagnosed. The incidence of both diseases is rising, demonstrating the inadequacy of current treatments which may be either ineffective or have toxicity risks including cardiovascular effects. Treatment of diabetes with sulfonylureas or insulin can cause hypoglycaemia, whilst metformin causes GI side-effects. No drug treatment for Type 2 diabetes has been shown to reduce the long-term complications of the disease. Insulin sensitisers will be useful for many diabetics, however they do not have an anti-obesity effect.

Rat sleep/EEG studies have also shown that central administration of orexin-A, an agonist of the orexin receptors, causes a dose-related increase in arousal, largely at the expense of a reduction in paradoxical sleep and slow wave sleep 2, when administered at the onset of the normal sleep period. Therefore antagonists of its receptor may be useful in the treatment of sleep disorders including insomnia.

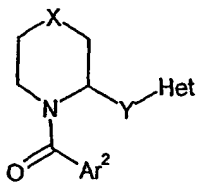
The present invention provides *N*-aroyl cyclic amine derivatives which are non-peptide antagonists of human orexin receptors, in particular orexin-1 receptors. In particular, these compounds are of potential use in the treatment of obesity, including obesity observed in Type 2 (non-insulin-dependent) diabetes patients, and/or sleep disorders Additionally these compounds are useful in stroke, particularly ischemic or haemorrhagic stroke, and/or blocking the emetic response i.e. the compounds are useful in the treatment of nausea and vomiting.

International Patent Applications WO99/09024, WO99/58533, WO00/47577 and WO00/47580 disclose phenyl urea derivatives and WO00/47576 discloses quinolinyl cinnamide derivatives as orexin receptor antagonists.(2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-ylmethyl)piperazine is disclosed in EP899270 as a starting material in the preparation of compounds useful for therapy of functional and inflammatory disorders of the gastrointestinal tract. The compound is also disclosed as Example 6 in EP655442. EP655442 describes piperizine derivatives useful as Tachykinin antagonists. 1-Benzoyl-2-[(1H-indol-3-yl)methyl]piperazine is also disclosed therein.

(2R)-1-(3,5-dichlorobenzoyl)-2-[(1H-indol-3-yl)methyl]piperazine and (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-[1H-indol-3-yl)methyl]piperazine are used as starting materials/intermediates in WO9857954.

(2R)-2-[1H-indol-3-yl)methyl]-1-[3-methoxy-5-trifluoromethyl)benzoyl]piperazine, is disclosed as a prepared by preparation 42 in WO00/35915.

According to the invention there is provided a compound of formula (I):



(I)

wherein:

X represents a bond, oxygen, NR^3 or a group $(CH_2)_n$, wherein n represents 1, 2 or 3;

Y represents CH_2, CO, CH(OH), or $CH_2CH(OH)$;

Het is an optionally substituted bicyclic heteroaryl group containing up to 4 heteroatoms selected from N, O and S;

Ar^2 represents an optionally substituted phenyl or a 5- or 6-membered heterocyclyl group containing up to 3 heteroatoms selected from N, O and S, wherein the phenyl or heterocyclyl group is substituted by R^1 and further optional substituents; or Ar^2 represents an optionally substituted bicyclic aromatic or bicyclic heteroaromatic group containing up to 3 heteroatoms selected from N, O and S;

R^1 represents hydrogen, optionally substituted(C_{1-4})alkoxy, halo, cyano, optionally substituted(C_{1-6})alkyl, optionally substituted phenyl, or an optionally substituted 5- or 6-membered heterocyclyl group containing up to 4 heteroatoms selected from N, O and S;

R^3 represents hydrogen or an optionally substituent (C_{1-4})alkyl other than when Het is indolyl where R^3 represents hydrogen or (C_{1-4}) alkyl;

or a pharmaceutically acceptable salt thereof.

with the proviso that;

when X is NH, Y is CH_2 and Het is indolyl, Ar^2 is not 3,5-bis(trifluoromethyl)phenyl;

or the compound is not

(2R)-1-(3,5-dichlorobenzoyl)-2-[(1H-indol-3-yl)methyl]piperazine;

(2R)-2-[1H-indol-3-yl)methyl]-1-[3-methoxy-5-trifluoromethyl)benzoyl]piperazine; or

1-benzolyl-2-[1H-indol-3-yl)methyl]piperazine.

Preferably where Ar^2 represents phenyl or a 5- or 6-membered heterocyclyl group containing up to 3 heteroatoms selected from N, O and S, the R^1 group is situated adjacent to the point of attachment to the amide carbonyl.

X is preferably a bond, oxygen or CH_2, NH or NMe, more preferably CH_2, NH or NMe, most preferably CH_2.

Alternatively X is preferably a bond, oxygen or $(CH_2)n$ wherein n is 1 or 2.

Y is preferably CH_2.

Preferably R^3 is hydrogen or a (C_{1-4})alkyl.

Het may have up to 5, preferably 1, 2 or 3 optional substituents.

Examples of when Het is an optionally substituted bicyclic heteroaryl group are quinoxalinyl, quinazolinyl, pyridopyrazinyl, benzoxazolyl, benzothienyl, benzofuranyl, benzimidazolyl, naphthyridinyl or benzothiazolyl. Additionally Het may be indolyl, triazolopyridinyl, furopyridinyl, pyridopyrimidinyl, isoquinolinyl or quinolinyl. Furthermore Het

can be oxazolylpyridinyl or tetrahydrobenzimidazolyl, tetrahydrobenzofuranyl, or tetrahydrotriazolopyridinyl.

Preferably Het is benzofuranyl, benzoxazolyl, benzimidazolyl, furopyridinyl, benzothiazolyl, indolyl, benzothienyl, triazolopyridinyl, quinolinyl and tetrahydrotriazolopyryidinyl, more preferably benzimidazolyl, benzofuranyl, benzoxazolyl, even more preferably benzofuranyl or benzimidazolyl.

When Ar^2 is a 5- or 6-membered heteroaryl group containing up to 3 heteroatoms selected from N, O and S, it may be furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, triazinyl, pyridazinyl, pyridinyl, pyrimidinyl, isothiazolyl, isoxazolyl, pyrazinyl or pyrazolyl.

More specifically, examples of Ar^2 are thiazolyl, pyrazolyl, triazolyl, pyridazinyl, oxazolyl, pyridinyl, pyrimidinyl, isoxazolyl and thienyl.

When R^1 is a 5- or 6-membered heterocyclyl group containing up to 4 heteroatoms selected from N, O and S, it may be furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyridinyl, triazolyl, triazinyl, pyridazinyl, pyrimidinyl, isothiazolyl, isoxazolyl, pyrazinyl or pyrazolyl. Additional heterocyclyl groups can be morpholinyl, piperazinyl and thiomorpholinyl. Furthermore it can be tetrazolyl, piperidinyl or pyrrolidinyl.

Preferably when R^1 is a 5- or 6-membered heterocyclyl group containing up to 4 heteroatoms selected from N, O and S, it may be oxadiazolyl, pyridinyl, pyrimidinyl, morpholinyl pyrazolyl or pyrrolyl.

Examples of where Ar^2 represents an optionally substituted bicyclic aromatic or bicyclic heteroaromatic include naphthyl, quinolinyl, napththyridinyl, benzofuranyl, benzimidazolyl, quinoxalinyl or quinazolinyl. Additionally Ar^2 may be isoquinolinyl or benzoxazolyl. Furthermore it can benzotriazolyl, benzothienyl, indolyl, benzothiazolyl, or benzothiadiazolyl.

Preferably Ar^2 represents optionally substituted phenyl, pyridinyl, thiazolyl, pyrazolyl, pyridazinyl, thienyl, naphthyl, triazolyl, isoxazolyl, quinolinyl, or isoquinolinyl.

More preferably Ar^2 represents optionally substituted phenyl, pyridinyl, thiazolyl, pyrazolyl, thienyl, triazolyl, quinolinyl, or isoquinolinyl.

Even more preferably Ar^2 represents optionally substituted phenyl, pyridinyl, thiazolyl, pyrazolyl, thienyl, or 1,2,3-triazolyl.

Alternatively R^1 represents hydrogen, optionally substituted(C_{1-4})alkoxy, halo, optionally substituted(C_{1-6})alkyl, optionally substituted phenyl, or an optionally substituted 5- or 6-membered heterocyclyl group containing up to 3 heteroatoms selected from N, O and S.

Preferably R^1 represents optionally substituted(C_{1-4})alkoxy, halo, optionally substituted(C_{1-6})alkyl, optionally substituted phenyl, or an optionally substituted 5- or 6-membered heterocyclyl group containing up to 3 heteroatoms selected from N, O and S.

Even more preferably R^1 represents an optionally substituted phenyl, pyridinyl, pyrazolyl pyrimidinyl or oxadiazolyl group.

Optional substituents for the groups Het, Ar^2, R^1 and R^3 include halogen, hydroxy, oxo, cyano, nitro, (C_{1-4})alkyl, (C_{1-4})alkoxy, hydroxy(C_{1-4})alkyl, hydroxy(C_{1-4})alkoxy, halo(C_{1-4})alkyl, halo(C_{1-4})alkoxy, aryl(C_{1-4})alkoxy, (C_{1-4})alkylthio, hydroxy(C_{1-4})alkyl, (C_{1-4})alkoxy(C_{1-4})alkyl, (C_{3-6})cycloalkyl(C_{1-4})alkoxy, (C_{1-4})alkanoyl, (C_{1-4})alkoxycarbonyl, (C_{1-4})alkylsulfonyl, (C_{1-4})alkylsulfonyloxy, (C_{1-4})alkylsulfonyl(C_{1-4})alkyl, arylsulfonyl, arylsulfonyloxy, arylsulfonyl(C_{1-4})

$_4$)alkyl, (C_{1-4})alkylsulfonamido, (C_{1-4})alkylamido, (C_{1-4})alkylsulfonamido(C_{1-4})alkyl, (C_{1-4})alkylamido(C_{1-4})alkyl, arylsulfonamido, arylcarboxamido, arylsulfonamido(C_{1-4})alkyl, arylcarboxamido(C_{1-4})alkyl, aroyl, aroyl(C_{1-4})alkyl, or aryl(C_{1-4})alkanoyl group; a group R^aR^bN-, $R^aOCO(CH_2)_r$, $R^aCON(R^a)(CH_2)_r$, $R^aR^bNCO(CH_2)_r$, $R^aR^bNSO_2(CH_2)_r$ or $R^aSO_2NR^b(CH_2)_r$ where each of R^a and R^b independently represents a hydrogen atom or a (C_{1-4})alkyl group or where appropriate R^aR^b forms part of a (C_{3-6})azacyloalkane or (C_{3-6})(2-oxo)azacycloalkane ring and r represents zero or an integer from 1 to 4. Additional substituents are (C_{1-4})acyl, aryl, aryl(C_{1-4})alkyl, (C_{1-4})alkylamino(C_{1-4})alkyl, $R^aR^bN(CH_2)n$-, $R^aR^bN(CH_2)nO$-, wherein n represents an interger from 1 to 4. Additionally when the substituent is $R^aR^bN(CH_2)n$- or $R^aR^bN(CH_2)nO$, R^a with at least one CH_2 of the $(CH_2)n$ portion of the group form a (C_{3-6})azacycloalkane and R^b represents hydrogen, a (C_{1-4})alkyl group or with the nitrogen to which it is attached forms a second (C_{3-6})azacycloalkane fused to the first (C_{3-6})azacycloalkane.

Preferred optional substituents for Ar^2 are halogen, cyano, (C_{1-4})alkyl, hydroxy(C_{1-4})alkyl, (C_{1-4})alkoxy(C_{1-4})alkyl, $R^aR^bN(CH_2)n$ or R^aR^bN, more preferably halogen, cyano and (C_{1-4})alkyl. Additional substituents are (C_{1-4})acyl, $R^aR^bN(CH_2)nO$, (C_{1-4})alkoxy, phenyl, and (C_{1-4})alkylamido.

More preferred substituents for Ar^2 are (C_{1-4})alkyl, hydroxy(C_{1-4})alkyl, R^aR^bN, (C_{1-4})alkoxy, $R^aR^bN(CH_2)n$, (C_{1-4})acyl, and (C_{1-4})alkylamido.

Preferred optional substituents for Het are halogen, cyano, (C_{1-4})alkyl, hydroxy(C_{1-4})alkyl, (C_{1-4})acyl, (C_{1-4})alkoxy(C_{1-4})alkyl, $R^aR^bNCO(CH_2)_r$, $R^aR^bN(CH_2)n$, $R^aR^bN(CH_2)nO$ or R^aR^bN. Additional optional substituents are (C_{1-4})alkoxy or CF_3.

More preferred substituents for Het are halogen, $R^aR^bNCO(CH_2)_r$, cyano, (C_{1-4})alkoxy, (C_{1-4})alkyl, $R^aR^bN(CH_2)n$, hydroxy(C_{1-4})alkyl, (C_{1-4})acyl or (C_{1-4})alkoxy(C_{1-4})alkyl.

Preferred optional substituents for R^1 are halogen, (C_{1-4})alkoxy(C_{1-4})alkyl, R^aR^bN, $R^aR^bN(CH_2)nO$ or $R^aR^bN(CH_2)n$. Additional optional sustituents are (C_{1-4})alkyl, (C_{1-4})alkoxy and (C_{1-4})acyl.

More preferred substituents for R^1 are halogen, $R^aR^bN(CH_2)nO$, (C_{1-4})alkyl, and (C_{1-4})alkoxy.

Prefered optional substituents for R^3 may be selected from halogen, hydroxy, cyano, (C_{1-4})alkoxy, $R^aR^bN(CH_2)nO$ or R^aR^bN.

In the groups Het and Ar^2, substituents positioned *ortho* to one another may be linked to form a ring.

Illustrative compounds of formula (I) can be selected from:

1	(RS)-2-(2-Benzofuranylmethyl)-1-((5-(4-fluorophenyl)-2-methyl-thiazol-4-yl)-carbonyl)-piperidine
2	(RS)-1-(2-Benzooxazol-2-ylmethyl-piperidin-1-yl)-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
3	(RS)-1-(2-Benzooxazol-2-ylmethyl-piperidin-1-yl)-1-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone

and pharmaceutical acceptable salts thereof.

Additional compounds of formula (I) can be selected from:

4	(RS)-1-(2-Benzofuran-2-ylmethyl-piperidin-1-yl)-1-[4-(4-fluoro-phenyl)-1-methyl-1-*H*-pyrazol-3-yl]-methane
5	(RS)-1-[2-(5-Fluoro-benzofuran-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
6	(RS)-1-[2-(5-Fluoro-benzofuran-2-ylmethyl)-piperidin-1-yl]-1-(5-pyridin-2-yl-thiazol-4-yl)-methanone
7	(RS)-1-[2-(5-Fluoro-benzofuran-2-ylmethyl)-piperidin-1-yl]-1-quinolin-4-yl-methanone
8	(RS)-1-[2-(5-Fluoro-benzofuran-2-ylmethyl)-piperidin-1-yl]-1-quinolin-5-yl-methanone
9	(RS)-1-[2-(5-Fluoro-benzofuran-2-ylmethyl)-piperidin-1-yl]-1-(2-methoxy-pyridin-3-yl)-methanone
10	(RS)-1-[2-Dimethylamino-5-(4-fluoro-phenyl)-thiazol-4-yl]-1-[2-(5-fluoro-benzofuran-2-ylmethyl)-piperidin-1-yl]-methanone
11	(RS)-1-[2-(5-Fluoro-benzofuran-2-ylmethyl)-piperidin-1-yl]-1-(2-morpholin-4-yl-phenyl)-methanone
12	(RS)-1-[2-(5-Fluoro-benzofuran-2-ylmethyl)-piperidin-1-yl]-1-(2-trifluoromethoxy-phenyl)-methanone
13	(RS)-1-(2-Benzofuran-2-ylmethyl-piperidin-1-yl)-1-[2-(2-dimethylamino-ethoxy)-phenyl]-methanone
14	(RS)-1-(2-Benzofuran-2-ylmethyl-piperidin-1-yl)-1-quinolin-8-yl-methanone
15	(RS)-1-(2-Benzofuran-2-ylmethyl-piperidin-1-yl)-1-(2-pyrimidin-2-yl-phenyl)-methanone
16	(RS)-1-(2-Benzofuran-2-ylmethyl-piperidin-1-yl)-1-[5-(4-fluoro-phenyl)-2H-[1,2,3]triazol-4-yl]-methanone
17	(RS)-1-(2-Benzofuran-2-ylmethyl-piperidin-1-yl)-1-[4-(4-fluoro-phenyl)-1H-pyrazol-3-yl]-methanone
18	(RS)-1-(2-Benzofuran-2-ylmethyl-piperidin-1-yl)-1-[5-(4-fluoro-phenyl)-2-hydroxymethyl-thiazol-4-yl]-methanone
19	(RS)-1-(2-Benzofuran-2-ylmethyl-piperidin-1-yl)-1-isoquinolin-8-yl-methanone
20	(RS)-1-(2-Benzofuran-2-ylmethyl-piperidin-1-yl)-1-isoquinolin-5-yl-methanone
21	(RS)-1-(2-Benzofuran-2-ylmethyl-piperidin-1-yl)-1-{5-[3-(3-dimethylamino-propoxy)-phenyl]-2-methyl-thiazol-4-yl}-methanone
22	(RS)-1-(2-Benzofuran-2-ylmethyl-piperidin-1-yl)-1-{5-[3-(4-dimethylamino-butoxy)-phenyl]-2-methyl-thiazol-4-yl}-methanone
23	(RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-(2-furo[2,3-*b*]pyridin-2-ylmethyl-piperidin-1-yl)-methanone
24	(RS)-1-[4-(4-Fluoro-phenyl)-1-methyl-1*H*-pyrazole-3-yl]-(2-furo[2,3-*b*]pyridin-2-ylmethyl-piperidin-1-yl)methanone
25	(RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-(2-quinolin-2-ylmethyl-piperidin-1-yl)-methanone
26	(RS)-1-Benzofuran-2-yl-1-(1-{1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-piperidin-2-yl)-methanone
27	(RS)-1-[2-(1*H*-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
28	(RS)-1-[2-(5-Chloro-1H-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
29	(RS)-1-[2-(5-Fluoro-1H-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
30	(RS)-1-[2-(5-Chloro-6-fluoro-1H-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
31	(RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[2-(4-methyl-1H-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-methanone
32	(RS)-1-[2-(4,6-Difluoro-1H-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-

	fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
33	(RS)-1-[2-(4-Dimethylaminomethyl-1H-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
34	(RS)-1-[2-(5-Bromo-1H-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
35	(RS)-1-[2-(5,6-Difluoro-1*H*-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
36	(RS)-1-[2-(4,5-Difluoro-1*H*-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
37	(RS)-1-[2-(5,6-Difluoro-1*H*-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-hydroxymethyl-thiazol-4-yl]-methanone
38	(RS)-1-[2-(4,5-Difluoro-1*H*-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-hydroxymethyl-thiazol-4-yl]-methanone
39	(RS)-1-[2-(5,6-Difluoro-1*H*-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[4-(4-fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanone
40	(RS)-1-[2-(5-Methoxy-1*H*-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
41	(RS)-1-[2-(6,7-Difluoro-1H-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-(2-methyl-5-phenyl-thiazol-4-yl)-methanone
42	(RS)-1-[2-(6,7-Difluoro-1H-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[4-(4-fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanone
43	(RS)-1-[2-(6,7-Difluoro-1H-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[4-(4-fluoro-phenyl)-1H-pyrazol-3-yl]-methanone
44	(RS)-1-[2-(4,5-Difluoro-1H-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-{5-[3-(2-dimethylamino-ethoxy)-phenyl]-2-methyl-thiazol-4-yl}-methanone
45	(RS)-1-[2-(4,5-Difluoro-1H-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(2-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
46	(RS)-1-[2-(4,5-Difluoro-1H-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(3-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
47	(RS)-1-[2-(4,5-Difluoro-1H-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-(2-trifluoromethoxy-phenyl)-methanone
48	(RS)-1-[2-(4,5-Difluoro-1H-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-(2-ethoxy-phenyl)-methanone
49	(RS)-1-[2-(4,5-Difluoro-1H-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-(2,6-dimethoxy-phenyl)-methanone
50	(RS)-1-[2-(6,7-Difluoro-1H-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-(2-pyrazol-1-yl-phenyl)-methanone
51	(RS)-1-[2-(5,6-Difluoro-1H-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[4-(4-fluoro-phenyl)-1H-pyrazol-3-yl]-methanone
52	(RS)-1-[2-(5,6-Difluoro-1H-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone
53	(RS)-1-[2-(Difluoro-1H-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[1-(2-dimethylamino-ethyl)-4-(4-fluoro-phenyl)-1H-pyrazol-3-yl]-methanone
54	(RS)-1-[2-(5,6-Difluoro-1H-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-2H-[1,2,3]triazol-4-yl]-methanone
55	(RS)-1-[2-(5,6-Difluoro-1H-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-{2-[3-(3-dimethylamino-propoxy)-phenyl]-thiophen-3-yl}-methanone
56	(RS)-1-[2-(5,6-Difluoro-1-methyl-1*H*-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
57	1-[(S)-2-(1*H*-Benzoimidazol-2-ylmethyl)-pyrrolidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
58	1-[(S)-2-(5,6-Difluoro-1*H*-Benzoimidazol-2-ylmethyl)-pyrrolidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
59	1-[(S)-2-(5,6-Difluoro-1*H*-Benzoimidazol-2-ylmethyl)-pyrrolidin-1-yl]-1-[4-(4-fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]methanone
60	(RS)-1-(2-Benzothiazol-2-ylmethylpiperidin-1-yl)-1-[5-(4-fluorophenyl)-2-methylthiazol-4-yl]-methanone
61	(RS)-1-(2-Benzothiazol-2-ylmethylpiperidin-1-yl)-1-[4-(4-fluorophenyl)-1-methyl-

	1-*H*-pyrazol-3-yl]-methanone
62	(RS)-1-(2-Benzothiazol-2-ylmethylpiperidin-1-yl)-1-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)phenyl]-methanone
63	(RS)-1-[5-(4-Fluorophenyl)-2-methylthiazol-4-yl]-1-[2-(5,6,7,8-tetrahydro-[1,2,4]-triazolo[1,5-a]pyridin-2-ylmethyl)-piperidin-1-yl]-methanone
64	(RS)-1-[5-(4-Fluorophenyl)-2-methylthiazol-4-yl]-1-(2-[1,2,4]triazolo[1,5-a]pyridin-2-ylmethylpiperidin-1-yl)-methanone
65	1-[(RS)-2-((RS)-2-Benzofuran-2-yl-2-hydroxy-ethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone (as separate diastereoisomers)
66	(RS)-1-[2-(4-Bromo-1*H*-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluorophenyl)-2-methylthiazol-4-yl]methanone
67	(RS)-1-[2-(4-Cyano-1*H*-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluorophenyl)-2-methylthiazol-4-yl]methanone
68	(RS)-1-[2-(4-Acetyl-1*H*-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluorophenyl)-2-methylthiazol-4-yl]methanone
69	(RS)-2-(1-{1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-piperidin-2-ylmethyl)-1H-benzoimidazole-5-carbonitrile
70	(RS)-1-[2-(5,6-Difluoro-1-propyl-1*H*-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
71	(RS)-1-{2-[5,6-Difluoro-1-(2-methoxy-ethyl)-1*H*-benzoimidazol-2-ylmethyl]-piperidin-1-yl}-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
72	(RS)-1-{2-[1-(2-Dimethylamino-ethyl)-5,6-difluoro-1*H*-benzoimidazol-2-ylmethyl]-piperidin-1-yl}-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
73	(RS)-1-{2-[5,6-difluoro-1-(2-hydroxy-ethyl)-1*H*-benzoimidazol-2-ylmethyl]-piperidin-1-yl}-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
74	(RS)-1-[2-(6,7-Difluoro-1-methyl-1*H*-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluorophenyl)-2-methyl-thiazol-4-yl]-methanone
75	(RS)-1-[2-(4,5-Difluoro-1-methyl-1*H*-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluorophenyl)-2-methyl-thiazol-4-yl]-methanone
76	(RS)-2-(1-{1-[5-(4-Fluorophenyl)-2-methyl-thiazol-4-yl]-methanoyl}-piperidin-2-ylmethyl)-benzofuran-3-carboxylic acid amide
77	(RS)-2-(1-{1-[4-(4-Fluorophenyl)-1-methyl-1*H*-pyrazol-3-yl]-methanoyl}-piperidin-2-ylmethyl)-benzofuran-3-carboxylic acid amide
78	(RS)-1-[3-(4,5-Difluoro-1*H*-benzoimidazol-2-ylmethyl)-morpholin-4-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
79	(RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-(2-furo[3,2-b]-pyridin-2-ylmethyl-piperidin-1-yl)methanone
80	(RS)-1-[4-(4-Fluoro-phenyl)-1-methyl-1H-pyrazole-3-yl)-(2-furo[3,2-b]pyridin-2-ylmethyl-piperidin-1-yl)methanone
81	(RS)-1-[2-(3-Bromo-benzofuran-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
82	(RS)-2-(1-{1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-piperidin-2-ylmethyl)-benzofuran-3-carbonitrile
83	(RS)-1-[2-(5-Fluorobenzofuran-2-ylmethyl)-4-methylpiperazin-1-yl]-1-[5-(4-fluorophenyl)-2-methythiazol-4-yl]methanone
84	(RS)-1-(2-Benzofuran-2-ylmethyl-4-methyl-piperazin-1-yl)-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl)]-methanone
85	(RS)-1-(2-Benzofuran-2-ylmethyl-piperazin-1-yl)-1-[5-(4-fluorophenyl)-2-methyl-thiazol-4-yl]-methanone
86	1-{(RS)-2-[(RS)-1-(5-Fluoro-benzofurany-2-yl)-1-hydroxy-methyl]-4-methyl-piperazin-1-yl}-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
87	1-{(RS)-2-[(RS)-1-(5-Fluoro-benzofurany-2-yl)-1-hydroxy-methyl]-4-methyl-piperazin-1-yl}-1-(2-trifluoromethoxy-phenyl)-methanone
88	(RS)-1-[2-(1-{1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-piperidin-2-ylmethyl)-benzofuran-3-yl]-ethanone

89	(R)-1-[2-(5,6-Difluoro-1*H*-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoneand(S)-1-[2-(5,6-Difluoro-1*H*-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone

and pharmaceutically acceptable salts thereof.

Further compounds of formula (I) can be selected from

90	(RS)-1-(2-Benzofuran-2-ylmethyl-piperidin-1-yl)-1-[5-(4-methoxy-phenyl)-2-methyl-thiazol-4-yl]-methanone
91	(RS)-1-(2-Benzofuran-2-ylmethyl-piperidin-1-yl)-1-{5-[3-(2-dimethylamino-ethoxy)-phenyl]-2-methyl-thiazol-4-yl}-methanone
92	(RS)-1-[2-(4,5-Difluoro-1H-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone
93	1-[3-(2,6-Dichloro-phenyl)-5-methyl-isoxazol-4-yl]-1-[2-(4,5-difluoro-1H-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-methanone
94	(RS)-1-[2-(4,5-Difluoro-1H-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[4-(4-fluoro-phenyl)-2-methyl-2H-pyrazol-3-yl]-methanone
95	(RS)-1-[3-(2-Chloro-6-fluoro-phenyl)-5-methyl-isoxazol-4-yl]-1-[2-(4,5-difluoro-1H-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-methanone
96	(RS)-1-[3-(2-Chloro-phenyl)-5-methyl-isoxazol-4-yl]-1-[2-(4,5-difluoro-1H-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-methanone
97	(RS)-1-[2-(4,5-Difluoro-1H-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-(2-propoxy-phenyl)-methanone
98	(RS)-1-[2-(4,5-Difluoro-1H-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-(2-isopropoxy-phenyl)-methanone
99	(RS)-1-(2-Benzyloxy-phenyl)-1-[2-(4,5-difluoro-1H-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-methanone
100	(RS)-1-[2-(4,5-Difluoro-1H-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-(2-ethoxy-6-methoxy-phenyl)-methanone
101	(RS)-1-[2-(4,5-Difluoro-1H-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-(2-ethoxy-6-methyl-phenyl)-methanone
102	(RS)-1-(2,6-Diethoxy-phenyl)-1-[2-(4,5-difluoro-1H-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-methanone
103	1-(3-{1-[2-(4,5-Difluoro-1H-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-methanoyl}-4-ethoxy-phenyl)-ethanone
104	(RS)-1-[2-(4,5-Difluoro-1H-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-(2-ethoxy-naphthalen-1-yl)-methanone
105	(RS)-1-[2-(4,5-Difluoro-1H-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-(2-pyridin-2-yl-phenyl)-methanone
106	1-[2-(6,7-Difluoro-1H-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-(2-pyrrol-1-yl-phenyl)-methanone
107	(RS)-1-[2-(4,5-Difluoro-1H-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-{5-[3-(3-dimethylamino-propoxy)-phenyl]-2-methyl-thiazol-4-yl}-methanone
108	(RS)-1-[2-(4,5-Difluoro-1H-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-{5-[3-(4-dimethylamino-butoxy)-phenyl]-2-methyl-thiazol-4-yl}-methanone
109	(RS)-1-[2-(5,6-Difluoro-1H-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methoxy-thiazol-4-yl]-methanone
110	(RS)-1-[2-(5,6-Difluoro-1H-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[2-ethyl-5-(4-fluoro-phenyl)-thiazol-4-yl]-methanone
111	(RS)-1-[2-(5,6-Difluoro-1H-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(2-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
112	(RS)-1-[2-(5,6-Difluoro-1H-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(3-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
113	(RS)-1-[2-(4-Fluoro-1H-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
114	(RS)-1-[2-(4-Fluoro-1H-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[4-(4-fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanone

115	(RS)-1-[2-(4-Fluoro-1H-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[4-(4-fluoro-phenyl)-1H-pyrazol-3-yl]-methanone
116	(RS)-1-[2-(4-Fluoro-1H-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[4-(4-fluoro-phenyl)-2-methyl-2H-pyrazol-3-yl]-methanone
117	(RS)-1-(2-Ethoxy-phenyl)-1-[2-(4-fluoro-1H-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-methanone
118	(RS)-1-[2-(4-Fluoro-1H-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-hydroxymethyl-thiazol-4-yl]-methanone
119	(RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-{2-[4-(1-hydroxy-ethyl)-1*H*-benzoimidazol-2-ylmethyl]-piperidin-1-yl}-methanone
120	(RS)- 1-(2-Benzofuran-2-ylmethyl-piperidin-1-yl)-1-[5-(4-chloro-phenyl)-2-methyl-thiazol-4-yl]-methanone
121	(RS)-1-[2-(3-Chloro-furo[3,2-b]pyridin-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
122	(RS)-1-[2-(5,6-Difluoro-1-methyl-1*H*-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-hydroxymethyl-thiazol-4-yl]-methanone
123	(RS)-1-[2-(5-Chloro-benzofuran-2-ylmethyl)-4-methyl-piperazin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
124	(RS)-1-[2-(5-Chloro-benzofuran-2-ylmethyl)-piperazin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]- methanone
125	(RS)-1-[2-(5,7-Dichloro-benzofuran-2-ylmethyl)-4-methyl-piperazin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
126	(RS)-1-[2-(5,7-Dichloro-benzofuran-2-ylmethyl)-piperazin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4- yl]-methanone
127	(RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[2-(1H-indol-2-ylmethyl)-piperidin-1-yl]-methanone
128	(RS)-5-[1-(2-Benzofuran-2-ylmethyl-piperidin-1-yl)-methanoyl]-4*H*-benzo[1,4]oxazin-3-one
129	(RS)-1-[2-(5-Bromo-benzofuran-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
130	(RS)-1-[2-(5-Cyano-benzofuran-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
131	(RS)-1-[2-(4-Bromo-benzofuran-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
132	(RS)-1-[2-(4-Cyano-benzofuran-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
133	(RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[2-(3-methyl-benzofuran-2-ylmethyl)-piperidin-1-yl]-methanone
134	(RS)-1-[2-(4-Fluoro-benzofuran-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
135	(RS)-1-[2-(4-Fluoro-benzofuran-2-ylmethyl)-piperidin-1-yl]-1-[4-(4-fluoro-phenyl)-1-methyl-1H- pyrazol-3 -yl]-methanone
136	(RS)-1-[2-(4,6-Dichloro-benzofuran-2-ylmethyl)-4-methyl-piperazin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
137	(RS)-1-[2-(4,6-Dichloro-benzofuran-2-ylmethyl)-piperazin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4- yl]-methanone
138	(RS)-1-(2-Benzofuran-2-ylmethyl-pyrrolidin-1-yl)-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone

139	(RS)-1-(2-Benzofuran-2-ylmethyl-pyrrolidin-1-yl)-1-[4-(4-fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanone
140	(RS)- 1-(2-Benzo[b] thiophen-2-ylmethyl-piperidin-1-yl)-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
141	(RS)-1-(2-Benzo[b]thiophen-2-ylmethyl-piperidin-1-yl)-1-[4-(4-fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanone
142	(RS)-1-(2-Benzo[b]thiophen-2-ylmethyl-piperidin-1-yl)-1-quinolin-8-yl-methanone
143	(RS)-1-(2-Benzofuran-2-ylmethyl-piperidin-1-yl)-1-(2-methyl-5-phenyl-thiazol-4-yl)-methanone
144	1-[(S)-2-(5,6-Difluoro-1*H*-benzoimidazol-2-ylmethyl)-pyrrolidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-hydroxymethyl-thiazol-4-yl]-methanone
145	(RS)-1-(2-Benzofuran-2-ylmethyl-piperidin-1-yl)-1-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone
146	(R)-1-[2-(4,6-Difluoro-1*H*-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone and (S)-1-[2-(4,6-Difluoro-1*H*-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone

and pharmaceutically acceptable salts thereof.

When a halogen atom is present in the compound of formula (I) it may be fluorine, chlorine, bromine or iodine.

When the compound of formula (I) contains an alkyl group, whether alone or forming part of a larger group, e.g. alkoxy or alkylthio, the alkyl group may be straight chain, branched or cyclic, or combinations thereof, it is preferably methyl or ethyl.

When used herein the term aryl means a 5- to 6- membered ring for example phenyl, or a 7- to 12 membered bicyclic ring system where at least one of the rings is aromatic for example naphthyl.

When used herein the term bicyclic hetero aryl means a 7- to 12 membered bicyclic ring system where at least one of the rings is aromatic for example benzimidazoyl, or tetrahydrobenzimidazolyl.

It will be appreciated that compounds of formula (I) may exist as *R* or *S* enantiomers. The present invention includes within its scope all such isomers, including mixtures. Where additional chiral centres are present in compounds of formula (I), the present invention includes within its scope all possible diastereoismers, including mixtures thereof. The different isomeric forms may be separated or resolved one from the other by conventional methods, or any given isomer may be obtained by conventional synthetic methods or by stereospecific or asymmetric syntheses.

It will be understood that the invention includes pharmaceutically acceptable derivatives of compounds of formula (I) and that these are included within the scope of the invention.

Particular compounds according to the invention include those mentioned in the examples and their pharmaceutically acceptable derivatives.

As used herein "pharmaceutically acceptable derivative" includes any pharmaceutically acceptable salt, ester or salt of such ester of a compound of formula (I) which, upon administration to the recipient is capable of providing (directly or indirectly) a compound of formula (I) or an active metabolite or residue thereof.

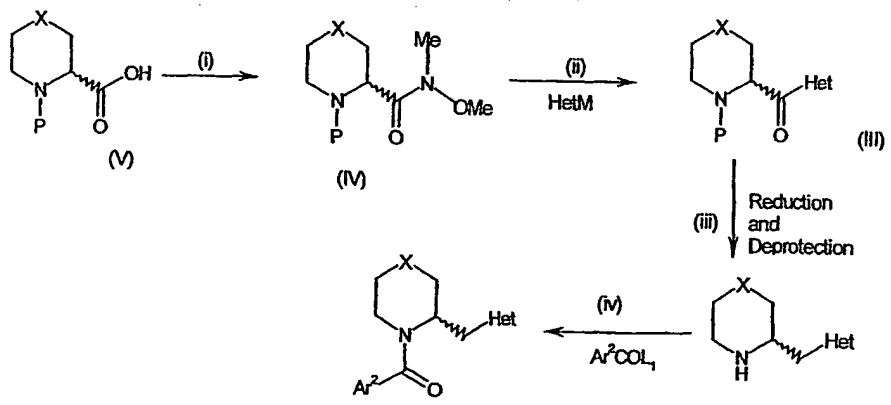
It will be appreciated that for use in medicine the salts of the compounds of formula (I) should be pharmaceutically acceptable. Suitable pharmaceutically acceptable salts will be apparent to those skilled in the art and include acid addition salts formed with inorganic acids e.g. hydrochloric, hydrobromic, sulphuric, nitric or phosphoric acid; and organic acids e.g. succinic, maleic, acetic, fumaric, citric, tartaric, benzoic, p-toluenesulfonic, methanesulfonic or naphthalenesulfonic acid. Other salts e.g. oxalates, may be used, for example in the isolation of compounds of formula (I) and are included within the scope of this invention. Also included within the scope of the invention are solvates and hydrates of compounds of formula (I).

Certain of the compounds of formula (I) may form acid addition salts with one or more equivalents of the acid. The present invention includes within its scope all possible stoichiometric and non-stoichiometric forms.

Since the compounds of formula (I) are intended for use in pharmaceutical compositions it will readily be understood that they are each preferably provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure and preferably at least 85%, especially at least 98% pure (% are on a weight for weight basis). Impure preparations of the compounds may be used for preparing the more pure forms used in the pharmaceutical compositions.

According to a further feature of the invention there is provided a process for the preparation of compounds of formula (I) and salts thereof. The following schemes detail some synthetic routes to compounds of the invention.

Scheme 1



wherein, X, Het, and Ar^2 are as defined for compounds of formula (I), P is a protecting group and M is a metal for example lithium.

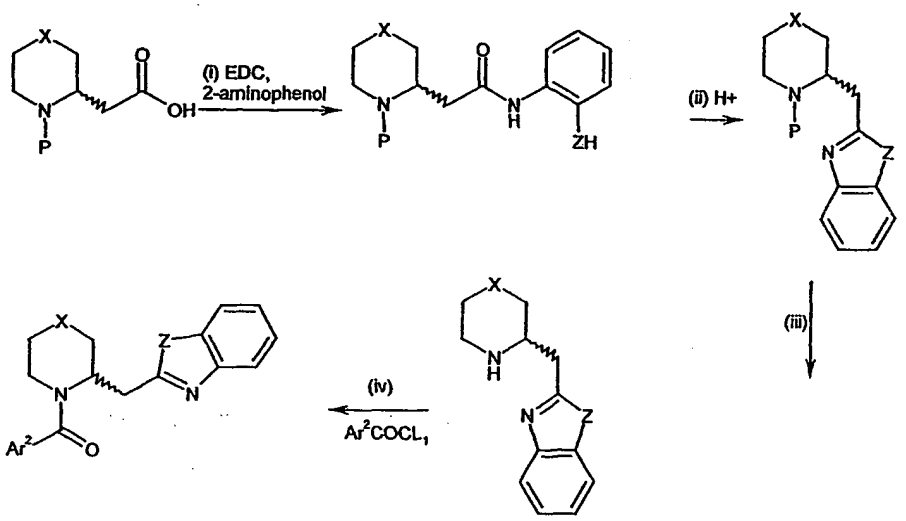
Examples of suitable leaving groups L_1 include halogen, OC(=O)alkyl and OC(=O)O-alkyl. The transformation (II) to (I) may be carried out in an inert solvent such as dichloromethane, in the presence of a base such as triethylamine. Alternatively this step may be carried out when L^1 represents hydroxy, in which case reaction with (II) takes place in an inert solvent such as dichloromethane in the presence of a diimide reagent such as 1-ethyl-3-(3-

dimethylaminopropyl)carbodiimide hydrochloride, and an activator such as 1-hydroxybenzotriazole.

Examples of protecting groups P include *t*-butyloxycarbonyl, trifluoroacetyl and benzyloxycarbonyl. Deprotection conditions are respectively, acid (e.g. trifluoroacetic acid in dichloromethane), base (e.g. sodium hydroxide in a solvent such as aqueous methanol) and catalytic hydrogenolysis in an inert solvent (e.g using palladium on charcoal in a lower alcohol or ethyl acetate).

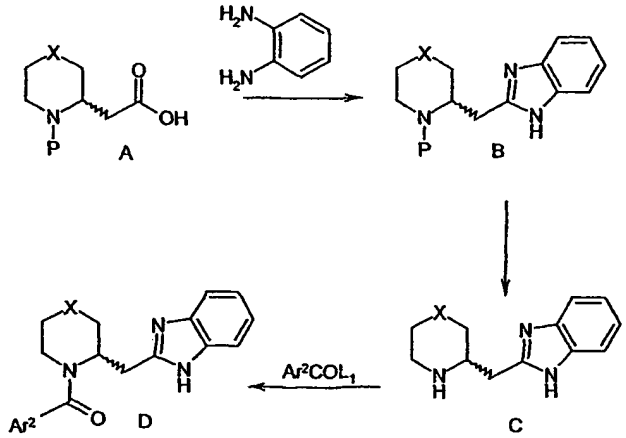
Compounds of formula (V) are known in the literature or can be prepared by known methods.

Scheme 2



wherein, X, and Ar^2 are as defined for compounds of formula (I), Z is S, or O, and P is a protecting group.

Scheme 3



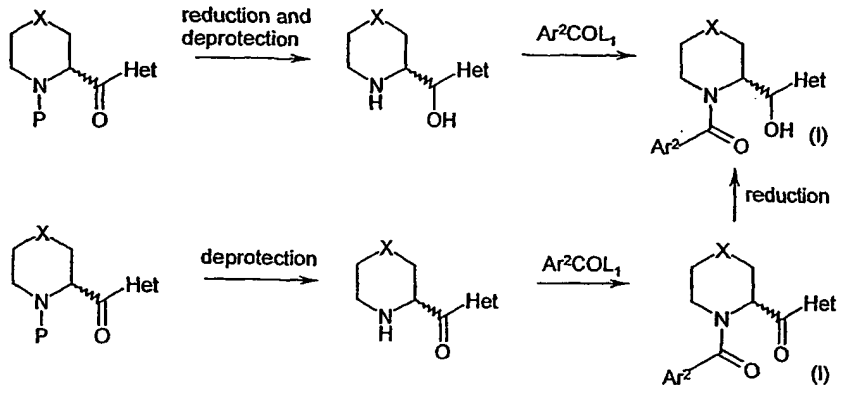
wherein, X, and Ar^2 are as defined for compounds of formula (I) and P is a protecting group.

Examples of protecting groups P include *t*-butyloxycarbonyl, trifluoroacetyl and benzyloxycarbonyl. Deprotection conditions are respectively, acid (e.g. trifluoroacetic acid in dichloromethane), base (e.g. sodium hydroxide in a solvent such as aqueous methanol) and catalytic hydrogenolysis in an inert solvent (e.g using palladium on charcoal in a lower alcohol or ethyl acetate).

The transformation of A to B can be carried out at elevated temperature in the absence of solvent or in the presence of an acid such as sulfuric acid or polyphosphoric acid, usually at elevated temperature. Deprotection can occur in situ under acidic conditions, if for example P is t-butoxycarbonyl to afford C directly.

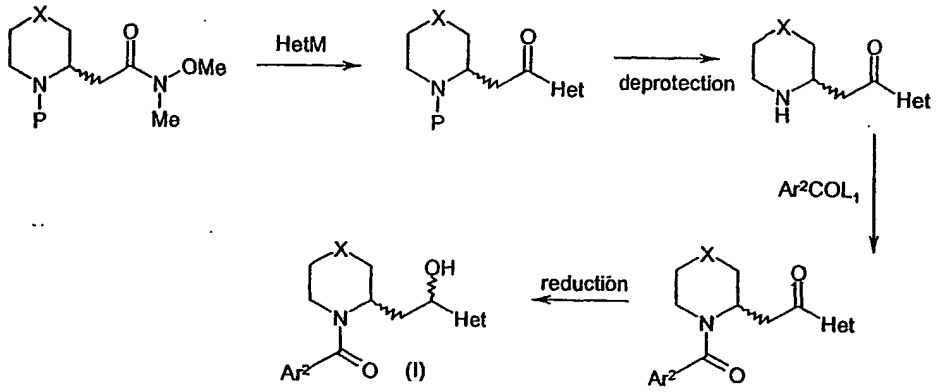
Examples of suitable leaving groups L_1 include halogen, OC(=O)alkyl and OC(=O)O-alkyl. The transformation C to D may be carried out in an inert solvent such as dichloromethane, in the presence of a base such as triethylamine. Alternatively this step may be carried out when L_1 represents hydroxy, in which case reaction with C takes place in an inert solvent such as dichloromethane in the presence of a diimide reagent such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, and an activator such as 1-hydroxybenzotriazole. Also when L_1 represents hydroxy the reaction can be effected using O-(7-azabenzotrazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) with a base such as triethylamine or N,N-diisopropylethylamine.

Scheme 4



Wherein Het, X and Ar^2 are as defined for formula I and P is a protecting group. Suitable reducing agents include sodium borohydride which can be used at ambient temperature in methanol.

Scheme 5



Wherein Het, X and Ar^2 are as defined for formula I, P is a protecting group and M is a metal for example lithium.

Within the schemes above there is scope for functional group interconversion; conversion of one compound of formula (I) to another of formula (I) by interconversion of substituents.

The compounds of formula (I) may be prepared singly or as compound libraries comprising at least 2, e.g. 5 to 1000, preferably 10 to 100 compounds of formula (I). Compound libraries may be prepared by a combinatorial 'split and mix' approach or by multiple parallel synthesis using either solution phase or solid phase chemistry, by procedures known to those skilled in the art.

Thus according to a further aspect of the invention there is provided a compound library comprising at least 2 compounds of formula (I), or pharmaceutically acceptable derivatives thereof.

Pharmaceutically acceptable salts may be prepared conventionally by reaction with the appropriate acid or acid derivative.

The compounds of formula (I) and their pharmaceutically acceptable derivatives are useful for the treatment of diseases or disorders where an antagonist of a human orexin receptor is required such as obesity and diabetes; prolactinoma; hypoprolactinemia; hypothalamic disorders of growth hormone deficiency; idiopathic growth hormone deficiency; Cushings syndrome/disease; hypothalamic-adrenal dysfunction; dwarfism; sleep disorders; sleep apnea; narcolepsy; insomnia; parasomnia; jet-lag syndrome; sleep disturbances associated with diseases such as neurological disorders, neuropathic pain and restless leg syndrome; heart and lung diseases; depression; anxiety; addictions; obsessive compulsive disorder; affective neurosis/disorder; depressive neurosis/disorder; anxiety neurosis; dysthymic disorder; behaviour disorder; mood disorder; sexual dysfunction; psychosexual dysfunction; sex disorder; sexual disorder; schizophrenia; manic depression; delerium; dementia; bulimia and hypopituitarism. The compounds of formula (I) or pharmaceutically acceptable derivatives thereof are also useful in the treatment of stroke, particular ischaemic or haemorrhagic stroke. Furthermore the compounds of formula (I) or pharmaceutically acceptable derivatives useful in the blocking an emetic response.

The compounds of formula (I) and their pharmaceutically acceptable derivatives are particularly useful for the treatment of obesity, including obesity associated with Type 2 diabetes, and sleep disorders. Additionally the compounds are useful in stroke and/or blocking the emetic response i.e. nausea and vomiting.

A further aspect of the invention is the use of
(2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-ylmethyl)piperazine;
(2R)-1-(3,5-dichlorobenzoyl)-2-[(1H-indol-3-yl)methyl]piperazine;
(2R)-2-[1H-indol-3-yl)methyl]-1-[3-methoxy-5-trifluoromethyl)benzoyl]piperazine; or
1-benzolyl-2-[1H-indol-3-yl)methyl]piperazine;
as an orexin antagonist.

Other diseases or disorders which may be treated in accordance with the invention include disturbed biological and circadian rhythms; adrenohypophysis disease; hypophysis disease; hypophysis tumor / adenoma; adrenohypophysis hypofunction; functional or psychogenic amenorrhea; adrenohypophysis hyperfunction; migraine; hyperalgesia; pain; enhanced or exaggerated sensitivity to pain such as hyperalgesia, causalgia and allodynia; acute pain; burn pain; atypical facial pain; neuropathic pain; back pain; complex regional pain syndromes I and II; arthritic pain; sports injury pain; pain related to infection e.g. HIV, post-polio syndrome and post-herpetic neuralgia; phantom limb pain; labour pain; cancer pain; post-chemotherapy pain; post-stroke pain; post-operative pain; neuralgia; and tolerance to narcotics or withdrawal from narcotics.

The invention also provides a method of treating or preventing diseases or disorders where an antagonist of a human orexin receptor is required, which comprises administering to a subject in need thereof an effective amount of a compound of formula (I), or a pharmaceutically acceptable derivative thereof.

The invention also provides a compound of formula (I), or a pharmaceutically acceptable derivative thereof, for use in the treatment or prophylaxis of diseases or disorders where an antagonist of a human orexin receptor is required.

The invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable derivative thereof, in the manufacture of a medicament for the treatment or prophylaxis of diseases or disorders where an antagonist of a human orexin receptor is required.

A further aspect of the invention is the use of (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-ylmethyl)piperazine in the manufacture of a medicament for the treatment or prophylaxis of diseases or disorders where an antagonist of a human orexin receptor is required.

For use in therapy the compounds of the invention are usually administered as a pharmaceutical composition. The invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable derivative thereof, and a pharmaceutically acceptable carrier.

The compounds of formula (I) and their pharmaceutically acceptable derivatives may be administered by any convenient method, e.g. by oral, parenteral, buccal, sublingual, nasal, rectal or transdermal administration, and the pharmaceutical compositions adapted accordingly.

The compounds of formula (I) and their pharmaceutically acceptable derivatives which are active when given orally can be formulated as liquids or solids, e.g. as syrups, suspensions, emulsions, tablets, capsules or lozenges.

A liquid formulation will generally consist of a suspension or solution of the active ingredient in a suitable liquid carrier(s) e.g. an aqueous solvent such as water, ethanol or glycerine, or a non-aqueous solvent, such as polyethylene glycol or an oil. The formulation may also contain a suspending agent, preservative, flavouring and/or colouring agent.

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations, such as magnesium stearate, starch, lactose, sucrose and cellulose.

A composition in the form of a capsule can be prepared using routine encapsulation procedures, e.g. pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), e.g. aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule.

Typical parenteral compositions consist of a solution or suspension of the active ingredient in a sterile aqueous carrier or parenterally acceptable oil, e.g. polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

Compositions for nasal administration may conveniently be formulated as aerosols, drops, gels and powders. Aerosol formulations typically comprise a solution or fine suspension of the active ingredient in a pharmaceutically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container which can take the form of a cartridge or refill for use with an atomising device. Alternatively the sealed container may be a disposable dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve. Where the dosage form comprises an aerosol dispenser, it will contain a propellant which can be a compressed gas e.g. air, or an organic propellant such as a fluorochlorohydrocarbon or hydrofluorocarbon. Aerosol dosage forms can also take the form of pump-atomisers.

Compositions suitable for buccal or sublingual administration include tablets, lozenges and pastilles where the active ingredient is formulated with a carrier such as sugar and acacia, tragacanth, or gelatin and glycerin.

Compositions for rectal administration are conveniently in the form of suppositories containing a conventional suppository base such as cocoa butter.

Compositions suitable for transdermal administration include ointments, gels and patches.

Preferably the composition is in unit dose form such as a tablet, capsule or ampoule.

The dose of the compound of formula (I), or a pharmaceutically acceptable derivative thereof, used in the treatment or prophylaxis of the abovementioned disorders or diseases will vary in the usual way with the particular disorder or disease being treated, the weight of the subject and other similar factors. However, as a general rule, suitable unit doses may be 0.05 to 1000 mg, more suitably 0.05 to 500 mg. Unit doses may be administered more than once a day for example two or three times a day, so that the total daily dosage is in the range of about 0.01 to 100 mg/kg; and such therapy may extend for a number of weeks or months. In the case of pharmaceutically acceptable derivatives the above figures are calculated as the parent compound of formula (I).

No toxicological effects are indicated/expected when a compound of formula (I) is administered in the above mentioned dosage range.

Human orexin-A has the amino acid sequence:

pyroGlu Pro Leu Pro Asp Cys Cys Arg Gln Lys Thr Cys Ser Cys Arg Leu
1 5 10 15
Tyr Glu Leu Leu His Gly Ala Gly Asn His Ala Ala Gly Ile Leu Thr

20 25 30

Leu-NH_2

Orexin-A can be employed in screening procedures for compounds which inhibit the ligand's activation of the orexin-1 receptor.

In general, such screening procedures involve providing appropriate cells which express the orexin-1 receptor on their surface. Such cells include cells from mammals, yeast, Drosophila or *E. coli*. In particular, a polynucleotide encoding the orexin-1 receptor is used to transfect cells to express the receptor. The expressed receptor is then contacted with a test compound and an orexin-1 receptor ligand to observe inhibition of a functional response. One such screening procedure involves the use of melanophores which are transfected to express the orexin-1 receptor, as described in WO 92/01810.

Another screening procedure involves introducing RNA encoding the orexin-1 receptor into *Xenopus* oocytes to transiently express the receptor. The receptor oocytes are then contacted with a receptor ligand and a test compound, followed by detection of inhibition of a signal in the case of screening for compounds which are thought to inhibit activation of the receptor by the ligand.

Another method involves screening for compounds which inhibit activation of the receptor by determining inhibition of binding of a labelled orexin-1 receptor ligand to cells which have the receptor on their surface. This method involves transfecting a eukaryotic cell with DNA encoding the orexin-1 receptor such that the cell expresses the receptor on its surface and contacting the cell or cell membrane preparation with a compound in the presence of a labelled form of an orexin-1 receptor ligand. The ligand may contain a radioactive label. The amount of labelled ligand bound to the receptors is measured, e.g. by measuring radioactivity.

Yet another screening technique involves the use of FLIPR equipment for high throughput screening of test compounds that inhibit mobilisation of intracellular calcium ions, or other ions, by affecting the interaction of an orexin-1 receptor ligand with the orexin-1 receptor.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The following Examples illustrate the preparation of pharmacologically active compounds of the invention. The Descriptions D1-D 83 illustrate the preparation of intermediates to compounds of the invention.

In the Examples ^{1}H NMR's were measured at 250MHz in $CDCl_3$ unless otherwise stated.
The following abbreviations are used herein;
PyBop means benzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate
THF means tetrahyrdofuran
EDC.HCL means 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
HATU means O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
TFA means trifluoroacetatic acid
DMF means N,N-dimethylformamide
DME means 1,2-dimethoxyethane

Description 1: (RS)-1-(*tert*-butyloxycarbonyl)-2-(N-methoxy-N-methylcarbamoyl)-piperidine

To (RS)-1-(*tert*-butyloxycarbonyl)-2-piperidine carboxylic acid (2.64 g, 11.5 mmol) in dichloromethane (10 ml) was added sequentially N,O-dimethyl hydroxylamine (1.34 g, 13.7 mmol), triethylamine (6 ml, 43.0 mmol) and Py.Bop (6.60 g, 12.7 mmol). The resultant mixture was stirred at ambient temperature for 6 h, then diluted with dichloromethane (170 ml) and poured into 1M HCl (22 ml). The organic phase was separated and washed with saturated aqueous sodium hydrogen carbonate (3 x 25 ml) and brine (25 ml) then evaporated *in vacuo*. The resultant colourless oil was chromatographed on silica gel eluting with 20 % ethyl acetate in hexane to give the title compound (2.43 g, 77 %) as a colourless oil.

Mass spectrum (API^+): Found 273 (MH^+). $C_{13}H_{24}N_2O_4$ requires 272.

Description 2: (RS)-2-(2-Benzofuranylcarbonyl)-1-(*tert*-butyloxycarbonyl)piperidine

To a solution of benzofuran (0.37 ml, 3.36 mmol) in THF (40 ml) at -35°C was added *n*butyllithium (1M in THF) (3.34 ml, 3.34 mmol) over 3 min. The resultant mixture was stirred for 10 min. at -35°C then (RS)-1-(*tert*-butyloxycarbonyl)-2-(N-methoxy-N-methylcarbamoyl)-piperidine (1.0 g, 3.68 mmol) in THF (5 ml) was added over 1 min. and the resultant solution stirred for 15 min. at -35°C. The mixture was poured into saturated ammonium chloride (20 ml) and extracted with ethyl acetate (3 x 20 ml). The combined organics were washed with saturated aqueous sodium hydrogen carbonate (15 ml), then evaporated *in vacuo*. The resultant residue was chromatographed on silica gel eluting with 10 % ethyl acetate in hexane to give the title compound (0.32 g, 26 %) as a yellow solid.

Mass spectrum (API^+): Found 330 (MH^+) $C_{19}H_{23}NO_4$ requires 329.

Description 3: (RS)-2-(2-Benzofuranylmethyl)piperidine

To a solution of (RS)-2-(2-benzofuranylcarbonyl)-1-(*tert*-butyloxycarbonyl)piperidine (0.30 g, 0.91 mmol) in diethylene glycol (20 g), was added hydrazine hydrate (0.16 ml, 2.79 mmol) and the resultant mixture heated at 170°C for 30 min. then cooled to room temperature. Potassium hydroxide (0.44 g, 7.86 mmol) was added and the mixture heated at 200°C for 18 h. The resultant was then poured into water (100 ml) and extracted with diethyl ether (3 x 20 ml). The combined organic extracts were dried (Na_2SO_4) and evaporated *in vacuo* to give the title compound (10 mg, 36 %) as a golden oil.

Mass spectrum (API^+). Found 216 (MH^+) $C_{14}H_{17}NO$ requires 215.

Description 4: (RS)-2-[(2-Hydroxy-phenylcarbamoyl)-methyl]-piperidine-1-carboxylic acid *tert* butyl ester

A mixture of 2-carboxymethyl-piperidine-1-carboxylic acid tert butyl ester (0.97g), (*Peschke, Bernd; Ankersen, Michael; Hansen, Birgit Sehested; Hansen, Thomas Kruse; Johansen, Nils Langeland; Lau, Jesper; Madsen, Kjeld; Petersen, Hans; Thogersen, Henning; Watson, Brett. Eur. J. Med. Chem. (1999), 34(5), 363-380*) in dimethylformamide (8.0ml) was treated sequentially with EDC.HCl (0.76g), 2-aminophenol (0.43g) and 1-hydroxybenzotriazole (0.05g). The mixture was stirred for 2h, diluted with ethyl acetate and washed with water, dried ($MgSO_4$) and solvent removed at reduced pressure to give the title compound (1.29g) as a gum.

Mass Spectrum (API$^+$): Found 335 (MH^+). $C_{18}H_{26}N_2O_4$ requires 334

Description 5 (RS)-2-Benzooxazol-2-ylmethyl-piperidine-1-carboxylic acid tert butyl ester
(RS)-2-[(2-Hydroxy-phenylcarbamoyl)-methyl]-piperidine-1-carboxylic acid *tert* butyl ester (1.25g), 4-toluenesulphonic acid (0.07g) and 4-N,N-dimethylaminopyridine (0.023g) were combined in 1, 3-dichlorobenzene (30ml) and the mixture boiled for 48h. The mixture was diluted with dichloromethane and washed with water. The organic phase was dried ($MgSO_4$) and solvent removed at reduced pressure. The residue was column chromatographed (silica gel, 0 → 1% methanol in dichloromethane) to give the title compound (0.50g)
Mass Spectrum (API$^+$): Found 317 (MH^+). $C_{18}H_{24}N_2O_3$ requires 316.

Description 6: (RS)-2-Piperidin-2-ylmethyl-benzooxazole
(RS)-2-Benzooxazol-2-ylmethyl-piperidine-1-carboxylic acid tert butyl ester (0.50g) in dichloromethane (8ml) was cooled (ice-bath) and trifluoroacetic acid (2ml) added. The mixture was stirred with ice-cooling for 4h, poured onto saturated potassium carbonate (20ml) and extracted with dichloromethane. The combined extracts were dried ($MgSO_4$) and solvent removed at reduced pressure to give the title compound (0.10g)
Mass Spectrum (API$^+$): Found 217 (MH^+). $C_{13}H_{16}N_2O$ requires 216.

Description 7: (RS)-2-[1-(5-Fluoro-benzofuran-2-yl)methanoyl)-piperidine-1-carboxylic acid *tert*-butyl ester
The title compound was prepared using the method of Description 2, from 5-fluorobenzofuran (1.36g, 10mmol, for preparation see WO99/51575), as a pale yellow solid (2.81g, 84%)
^{1}H NMR δ: 1.20-1.60 (11H, m), 1.60 - 1.85 (2H, m), 1.90 (1H, broad m), 2.15 - 2.30 (1H, broad m), 3.20 - 3.40 (1H, broad m), 3.85 - 4.05 (1H, broad m), 5.20 - 5.70 (1H, broad m), 7.10 - 7.25 (1H, m), 7.25 - 7.4 (1H, d, J = 7.4 Hz), 7.45 - 7.75 (2H, m).

Description 8: (RS)-2-(5-Fluoro-benzofuran-2-ylmethyl)-piperidine
The title compound was prepared using the method of Description 3, from (RS)-2-[1-(5-Fluoro-benzofuran-2-yl)methanoyl)-piperidine-1-carboxylic acid *tert*-butyl ester, D7 (1.21g, 3.49 mmol), as a pale yellow gum (0.72g, 89%).
Mass spectrum (API$^+$): Found 234 (MH^+) $C_{14}H_{16}FNO$ requires 233.

Description 9: (RS)-1-Benzofuran-2-yl-1-piperidin-2-yl-methanone
A solution of (RS)-2-(2-benzofuranylcarbonyl)-1-(*tert*-butyloxycarbonyl)piperidine, D2 (0.86g, 2.61 mmol) in trifluoroacetic acid (5ml) and dichloromethane (20ml) was warmed at 35°C for 0.5h. The reaction mixture was evaporated *in vacuo* and the residue partitioned between dichloromethane (30ml) and 1N sodium hydroxide (30ml). The aqueous layer was extracted with dichloromethane (30ml) and the combined organic layers dried (Na_2SO_4) and evaporated *in vacuo* to afford the title compound as a pale yellow gum (0.59g, 99%).
Mass spectrum (API$^+$): Found 230 (MH^+). $C_{14}H_{15}NO_2$ requires 229.

Description 10: (RS)-2-(1-Furo[2,3-*b*]pyridin-2-yl)methanoyl-piperidine-1-carboxylic acid *tert*-butyl ester

2.5N n-Butylithium in hexanes (2.3ml, 5.75mmol) was added dropwise over 10 min to a stirred solution of furo[2,3-*b*]pyridine (0.57g, 4.79mmol) (H. Sliwa, **Bull.Soc.Chim. France**, 646, 1970) in anhydrous THF (20ml) at -75°C under argon. The resultant mixture was stirred for 5 min at -70°C then a solution of (RS)-1-(*tert*-butyloxycarbonyl)-2-(N-methoxy-N-methylcarbamoyl)-piperidine, D1 (1.41g, 5.19mmol) in anhydrous THF (20ml) was added over 2 min. and the resultant solution stirred at -70°C for 15 min. The mixture was poured into saturated ammonium chloride (100ml) and extracted with ethyl acetate (2X50ml). The combined organics were dried (Na_2SO_4) and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with 0-1% ethyl acetate in dichloromethane to give the title compound as a colourless solid (0.51g, 32%).

^{1}H NMR δ: 1.25 - 1.55 (11H, m), 1.60 - 1.80 (2H, m), 1.85 - 2.05 (1H, broad m), 2.15 - 2.40 (1H, broad m), 3.15 - 3.40 (1H, broad m), 3.80 - 4.15 (1H, broad m), 5.35 - 5.65 (1H, broad m), 7.30 (1H, broad m), 7.56 (1H, broad s), 8.08 (1H, broad m), 8.53 (1H, broad m).

Description 11: (RS)-2-Piperidin-2-ylmethyl-furo[2,3-*b*]pyridine

The title compound was prepared using the method of Description 3, from (RS)-2-(1-furo[2,3-*b*]pyridin-2-yl)methanoyl)piperidine-1-carboxylic acid *tert*-butyl ester, D10 (0.51g, 1.55mmol), as a light brown gum (0.26g, 74%).

Mass spectrum (API$^+$): Found 217 (MH^+) $C_{13}H_{16}N_2O$ requires 216.

Description 12: (RS)-2-(1-Quinolin-2-yl-methanoyl)-piperidine-1-carboxylic acid *tert*-butyl ester

30% Potassium hydride dispersed in mineral oil (0.8g, 6mmol) was added to a stirred solution of 2-bromoquinoline (1.12g, 5.29mmol) (O. Sugimoto, **Tet. Lett.** 4, (1999), 7477-8) in anhydrous THF (20ml) at -70°C under argon. To this was added 2N n-butyllithium in hexanes (2.7ml, 6.75 mmol) dropwise over 5 min. The resultant mixture was stirred for 10 min at -70°C then a solution of (RS)-1-(*tert*-butyloxycarbonyl)-2-(N-methoxy-N-methylcarbamoyl)-piperidine, D1 (1.57g, 5.77mmol) in anhydrous THF (10ml) was added over 2 min. The cooling bath was removed and the reaction mixture allowed to warm to -20°C and held at -20°C for 10 min. The mixture was poured into saturated ammonium chloride (300ml) and extracted with ethyl actetate (2 x 100ml). The combined organics were dried (Na_2SO_4) and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with 0-10% ethyl acetate in pentane to yield the title compound as a pale yellow solid (1.2g, 66%).

^{1}H NMR δ: 1.2 -1.65 (12H, m), 1.65-1.85 (1H, m), 1.90-2.10 (1H, m), 2.20-2.50 (1H, m), 3.30-3.60 (1H, m), 3.85-4.20 (1H, m), 6.20-6.40 (1H, m), 7.50-7.90 (3H, m), 8.07 (1H, d, J = 8.4Hz), 8.18 (1H, d, J = 8.8Hz), 8.20-8.35 (1H, m).

Description 13: (RS)-2-Piperidin-2-ylmethyl-quinoline

The title compound was prepared using the method of Description 3, from (RS)-2-(1-quinolin-2-yl-methanoyl)-piperidine-1-carboxylic acid *tert*-butyl ester, D12 (1.2g, 3.66mmol), as a pale brown gum (0.053g, 6%)

Mass spectrum (Electrospray LC/MS): Found 227 (MH^+). $C_{15}H_{18}N_2$ requires 226.

Description 14: 2-Amino-*N,N*-dimethyl-3-nitro-benzamide

EDC.HCl (2.47 g, 12.88mmol) was added to a stirred mixture of 2-amino-3-nitrobenzoic acid (2.18g, 11.98mmol) (Mickelson, **J. Med. Chem**, 39(23) 4662 (1996)), 2M dimethylamine in THF (6.45ml, 12.9mmol) and 1-hydroxybenzotriazole (0.1g, 0.74 mmol) in dichloromethane (100 ml). The reaction mixture was stirred at room temperature for 18h, washed with saturated aqueous sodium bicarbonate and the organic layer dried (Na_2SO_4) and evaporated *in vacuo* to afford the title compound as a pale orange gum (2.5g, 100%).

^{1}H NMR δ: 3.08 (6H, s), 6.70 (1H, m), 6.85 (2H, broad s), 7.33 (1H, dd, J = 2 and 8Hz), 8.2 (1H, dd, J = 2 and 8Hz).

Description 15: 3-Dimethylaminomethyl-benzene-1,2-diamine

1M Lithium aluminium hydride in THF (18.1ml, 18.1mmol) was added dropwise over 5 min. to a stirred, ice cooled solution of 2-Amino-*N,N*-dimethyl-3-nitro-benzamide,D14 (1.26g, 6.03mmol) in anhydrous THF (40ml) under argon. The reaction mixture was stirred at 0°C for 0.5h then at room temperature for a further 2h before being recooled in ice, as water (3.2ml), 2N sodium hydroxide (3.6ml) and water (3.2ml) were added dropwise sequentially. The mixture was stirred for 10 min, solid Na_2SO_4 added and stirring continued for 10 min. Solids were filtered, washed with ethyl acetate and the combined organics evaporated *in vacuo* to give the title compound as an orange solid (0.9g, 91%).

^{1}H NMR δ: 2.19 (6H, s), 3.29 (2H, broad s), 3.42 (2H, s), 4.50 (2H, broad s), 6.50-6.80 (3H, m).

Description 16: (RS)-(1-{1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-piperidin-2yl)-acetic acid methyl ester

A stirring solution of 5-(4-fluoro-phenyl)-2-methyl-thiazole-4-carboxylic acid (3.00g, 12.5mmol) in DMF (50ml), under argon was treated sequentially with *N,N*-diisopropylethylamine (6.8ml), HATU (4.77g, 12.5mmol) then after stirring for 0.25h, piperidin-2-yl-acetic acid methyl ester (Beckett et al, J.Med.Chem., 563,1969) (1.83g, 12.5mmol) was added. The mixture was stirred for 16h at room temperature and was then diluted with water. The product was extracted into diethyl ether. The organic phase was washed with water (3X) and brine, was dried ($MgSO_4$) and the solvent removed *in vacuo* to afford the title compound as a yellow gum (4.00g, 85%).

Mass spectrum (API^+). Found 377 (MH^+). $C_{19}H_{21}FN_2O_3S$ requires 376.

Description 17: (RS)-(1-{1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-piperidin-2-yl)-acetic acid

A stirring solution of (1-{1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-piperidin-2yl)-acetic acid methyl ester, D16 (4.00g, 10.6mmol) in methanol/water (75ml/25ml) was treated with sodium hydroxide (0.85g, 21.3mmol). The mixture was stirred for 16h at room temperature. The methanol was removed *in vacuo* and the residue was diluted with water and extracted with diethyl ether (2X). The aqueous phase was acidified with 5N HCl and the product was extracted with ethyl acetate. The organic phase was dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was triturated with pentane to afford the title compound as a white solid (3.10g, 82%).

^{1}H NMR (D_6-DMSO) δ: 0.98 (0.6H, m), 1.15-1.70 (5.4H, bm), 2.18 (0.4H, dd), 2.38 (0.6H, dd, J = 6 and 15Hz), 2.70 (4.4H, m), 2.93 (0.6H, m), 3.17 (0.6H, d, J = 12Hz), 3.94 (0.4H, m), 4.40 (0.4H, d, J = 12Hz), 5.05 (0.6H, m), 7.27 (2H, m), 7.47 (2H, m), 12.20 (1H, bs).

Description 18: (RS)-5,6-Difluoro-2-piperidin-2-ylmethyl-1*H*-benzoimidazole

A mixture of 2-carboxymethyl-piperidine-1-carboxylic acid *tert*-butyl ester (Beckett et al, J.Med.Chem., 563,1969) (10.0g, 41mmol) and 4,5-difluoro-benzene-1,2-diamine (5.95g, 41mmol) in polyphosphoric acid (140g) was heated at 140°C for 7h. The cooled reaction mixture was poured onto excess solid potassium carbonate and crushed ice. The resulting basic, aqueous solution was extracted with ethyl acetate (2X) and the combined organics were washed with brine, dried (Na_2SO_4) and the solvent removed *in vacuo*. The residue was triturated with diethyl ether, ethyl acetate and pentane to afford the title compound as a light brown solid (7.14g, 69%).

^{1}H NMR (D_6-DMSO) δ: 1.08 (1H, m), 1.27 (2H, m), 1.50 (2H, m), 1.70 (1H, m), 2.48 (1H, m, obscured by DMSO), 2.78 (2H, d, J = 7Hz), 2.88 (2H, m), 7.51 (2H, app.t, J = 6Hz).

Description 19: (RS)-2-(5,6-Difluoro-1*H*-benzoimidazol-2-ylmethyl)-piperidine-1-carboxylic acid *tert*-butyl ester

4,5-Difluoro-benzene-1,2-diamine (1.00g, 6.9mmol) and 2-carboxymethyl-piperidine-1-carboxylic acid *tert*-butyl ester (Beckett et al, J.Med.Chem., 563,1969) (1.69g, 6.9mmol) were heated at 120°C with stirring, under argon for 4h. A further portion of 2-carboxymethyl-piperidine-1-carboxylic acid *tert*-butyl ester (0.85g) was added and heating was continued for a further 2h. The cooled reaction mixture was diluted with ethyl acetate, washed with saturated aqueous sodium bicarbonate (2X) and brine, dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was chromatographed (silica gel, 0-30% ethyl acetate-pentane) to give a yellow solid which was triturated with diethyl ether to afford the title compound as a pale brown solid (0.38g, 15%).

Mass spectrum (API$^+$). Found 352 (MH^+) $C_{18}H_{23}F_2N_3O_2$ requires 351.

Description 20: (RS)-5,6-Difluoro-2-piperidin-2-ylmethyl-1*H*-benzoimidazole. 2HCl

A stirring solution of 2-(5,6-Difluoro-1*H*-benzoimidazol-2-ylmethyl)-piperidine-1-carboxylic acid *tert*-butyl ester, D19 (375mg, 1.1mmol) in MeOH (20ml) was treated with 1M HCl in 1,4-dioxane (5ml). After stirring under argon at room temperature for 5h the volatiles were removed *in vacuo* to afford the title compound as a gum (100%).

Mass spectrum (API$^+$). Found 252 (MH^+) $C_{13}H_{15}F_2N_3$ requires 251.

Description 21: (RS)-4,5-Difluoro-2-piperidin-2-ylmethyl-1*H*-benzoimidazole

A mixture of 2-carboxymethyl-piperidine-1-carboxylic acid *tert*-butyl ester (Beckett et al, J.Med.Chem., 563,1969) (6.72g, 28mmol) and 3,4-difluoro-benzene-1,2-diamine (4.00g, 28mmol) in polyphosphoric acid (130g) was heated at 140°C for 7.5h. The cooled reaction mixture was poured onto excess solid potassium carbonate and crushed ice. The resulting basic, aqueous solution was extracted with ethyl acetate (2X) and the combined organics were washed with brine, dried (Na_2SO_4) and the solvent removed *in vacuo*. The residue was triturated with diethyl ether, ethyl acetate and pentane to afford the title compound as a white solid (4.29g, 62%).

^{1}H NMR (D_6-DMSO) δ: 1.08 (1H, m), 1.28 (2H, m), 1.50 (2H, m), 1.72 (1H, m), 2.46 (1H, m, obscured by DMSO), 2.81 (2H, d, J = 7Hz), 2.90 (2H, m), 7.14 (1H,m), 7.24 (1H, m).

Description 22: 1-(2-Dimethylamino-ethyl)-4-(4-fluoro-phenyl)-1*H*-pyrazole-3-carboxylic acid ethyl ester

4-(4-Fluoro-phenyl)-1*H*-pyrazole-3-carboxylic acid ethyl ester (2.4g, 10mmol) was added to an ice-cooled slurry of sodium hydride (0.82g, 60% dispersion in mineral oil, 20mmol) in DMF (20ml), under argon. *N,N*-diisopropylethylamine (1.8ml, 10mmol) was added followed by 2-chloro-ethyl dimethylamine.HCl (1.48g, 10mmol) and potassium iodide (5mg). The reaction mixture was stirred at room temperature for 16h then at 80°C for 48h. 2N HCl and water were added and the product extracted with ethyl acetate (3X). The combined organics were washed with brine, dried (Na_2SO_4) and the solvent removed *in vacuo*. Chromatography (silica gel, 3-10% methanol-dichloromethane) afforded 2-(2-dimethylamino-ethyl)-4-(4-fluoro-phenyl)-1*H*-pyrazole-3-carboxylic acid ethyl ester (900mg) and the title compound (630mg).
^{1}H NMR δ: 1.31 (3H, t. J = 7Hz), 2.29 (6H, s), 2.80 (2H, t, J = 6Hz), 4.30 (4H, m), 7.05 (2H, m), 7.44 (2H, m), 7.56 (1H, s).

Description 23: 1-(2-Dimethylamino-ethyl)-4-(4-fluoro-phenyl)-1*H*-pyrazole-3-carboxylic acid

A solution of 1-(2-Dimethylamino-ethyl)-4-(4-fluoro-phenyl)-1*H*-pyrazole-3-carboxylic acid ethyl ester, D22 (610mg, 2mmol) in methanol/water (15ml/10ml) was treated with 2N sodium hydroxide (4ml). After stirring at room temperature for 16h the methanol was removed *in vacuo* and the residue treated with 2N HCl (4ml). The water was removed *in vacuo*. Dichloromethane was added to the residue and the inorganic solid was removed by filtration. Removal of the solvent form the filtrate *in vacuo* afforded the title compound as a white solid (350mg, 63%).
Mass spectrum (API$^+$). Found 278 (MH^+) $C_{14}H_{16}FN_3O_2$ requires 277.

Description 24: 5-(4-Fluoro-phenyl)-2-methyl-2*H*-[1,2,3]triazole-4-carboxylic acid methyl ester

5-(4-Fluoro-phenyl)-2*H*-[1,2,3]triazole-4-carboxylic acid methyl ester (2.21g, 10mmol) in THF (10ml) was added drop-wise to an ice-cooled slurry of sodium hydride (0.42g, 60% dispersion in mineral oil, 10mmol) in THF (45ml), under argon. After stirring at room temperature for 1h, the reaction mixture was heated at 80°C for 16h. Water was added to the cooled mixture and the product was extracted with diethyl ether (2X). The combined organics were washed with brine, dried (Na_2SO_4) and the solvent removed *in vacuo*. Chromatography (silica gel, 10-50% ethyl acetate-pentane) afforded 5-(4-Fluoro-phenyl)-1-methyl-2*H*-[1,2,3]triazole-4-carboxylic acid methyl ester (763mg, 33%) and the title compound (943mg, 40%).
^{1}H NMR δ: 3.94 (3H, s), 4.29 (3H, s), 7.13 (2H, m), 7.87 (2H, m).

Description 25: 5-(4-Fluoro-phenyl)-2-methyl-2*H*-[1,2,3]triazole-4-carboxylic acid

5-(4-Fluoro-phenyl)-2-methyl-2*H*-[1,2,3]triazole-4-carboxylic acid methyl ester
D24 (940mg, 4mmol) in water (65ml) was treated with 2N sodium hydroxide (4ml) and the mixture was heated at 120°C for 2h. The volume of water was reduced to 20ml *in vacuo* and the

ice-cooled residue was treated with 2N HCl (4ml). Filtration, washing with water and drying *in vacuo* afforded the title compound as a white solid (810mg, 91%).
Mass spectrum (API^+). Found 222 (MH^+) $C_{10}H_8FN_3O_2$ requires 221.

Description 26: (S)-Pyrrolidin-2-ylmethyl-1H-benzoimidazole
A mixture of benzene-1,2-diamine (0.235g, 2.2mmol) and (S)-2-carboxymethyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.500g, 2.2mmol) in polyphosphoric acid (10g)was heated under argon at 140°C for 4h then at 160°C for 20h. The reaction mixture was cooled and partitioned between aqueous saturated potassium carbonate and dichloromethane. The aqueous phase was extracted with 9-1 dichloromethane-methanol (4X). The combined organics were dried ($MgSO_4$) and the solvent removed *in vacuo* to afford the title compound as a pale brown foam (0.328g) contaminated with ≈ 9% starting diamine.
^1H NMR δ: 1.30-2.10 (4H, bm), 2.80-3.60 (6H, bm incl.NH), 7.20 (1H, m), 7.55 (1H, m).

Description 27: (S)-5,6-Difluoro-pyrrolidin-2-ylmethyl-1H-benzoimidazole
A mixture of 4,5-difluorobenzene-1,2-diamine (0.360g, 2.5 mmol) and (S)-2-carboxymethyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.570g, 2.5 mmol) in polyphosphoric acid (9.5g) was heated under argon at 160°C for 20h. The reaction mixture was cooled and partitioned between aqueous saturated potassium carbonate and dichloromethane. The aqueous phase was extracted with 9-1 dichloromethane-methanol (4X). The combined organics were dried ($MgSO_4$) and the solvent removed at reduced pressure to afford the title compound as a pale brown foam (0.394g).
Mass Spectrum (API^+): Found 236 (M-H). $C_{12}H_{13}F_2N_3$ requires 237.

Description 28: (RS)-[1-(2,2,2-Trifluoroethanoyl)-piperidin-2-yl] acetic acid ethyl ester
(RS)-Piperidin-2-yl acetic acid ethyl ester (Rhodes et al, J.Am.Pharm.Assoc.,1956,45,746) (6.0g) was dissolved in dry dichloromethane (60 ml) and cooled to –10 °C under an atmophere of argon. Triethylamine (5.0ml), followed by trifluoroacetic anhydride (5.1ml) was added to the stirred solution and stirring was continued at room temperature for 16h. The reaction solution was then partitioned between dichloromethane and saturated sodium bicarbonate solution. The organic solution was dried ($MgSO_4$) and the solvent removed *in vacuo* to yield the title compound as an oil (4.2 g).
Mass Spectrum (API^+): Found 268 (MH^+). $C_{11}H_{16}F_3NO_3$ requires 267.

Description 29:(R.S)-1-(2-Benzothiazol-2-ylmethylpiperidin-1-yl)-2,2,2-trifluoro-ethanone
[1-(2,2,2-Trifluoroethanoyl)piperidin-2-yl] acetic acid ethyl ester, D28 (1.34g) and 2-aminothiophenol (1.50g) were suspended in polyphosphoric acid (30ml) and heated to 90°C for 2h with vigorous stirring. After cooling, the reaction mixture was poured into iced water and stirred vigorously for 1h. The aqueous solution was then extracted several times with ethyl acetate. After drying ($MgSO_4$), the solvent was removed *in vacuo* and the residue chromatographed (silica gel) to afford the title compound as an oil (1.2g).
Mass Spectrum (API^+): Found 329 (MH^+). $C_{15}H_{15}F_3N_2SO$ requires 328.

Description 30:(RS)-2-Piperidin-2-ylmethylbenzothiazole

1-(2-Benzothiazol-2-ylmethylpiperidin-1-yl)-2,2,2-trifluoroethanone, D29 (1.2g) was dissolved in methanol (40ml) and 2N sodium hydroxide solution (20ml) and heated to 50 °C for 0.75h. After cooling, the reaction solution was partitioned between dichloromethane and water. The organic solution was dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was chromatographed (silica gel, 0-10% [9:1 MeOH/conc. ammonia solution] in dichloromethane) to afford the title compound (0.68 g).
Mass Spectrum (API$^+$): Found 233 (MH^+). $C_{13}H_{16}N_2S$ requires 232.

Description 31: (RS)- 1-Benzyl-2-bromomethylpiperidine
(RS)-(1-Benzyl-piperidin-2-yl)-methanol (R.Sreekumar et al, Tetrahedron Lett., 1998, 39 5151) (10.0g) was converted to the title compound (5.2g) by treatment with triphenylphosphine (13.0g) and N-bromosuccinimide (9.4g) in dichloromethane using literature procedures, (Tetrahedron Lett,, 1999, **40**, 7477-8).
Mass Spectrum (API$^+$): Found 270 (MH^+). $C_{13}H_{18}{}^{81}BrN$ requires 269.

Description 32: (RS)-1-Benzyl-2-cyanomethylpiperidine
(RS)-1-Benzyl-2-bromomethylpiperidine, D31 (4.2g) was dissolved in dry dimethylsulphoxide (15ml) and treated with sodium cyanide (5.0g). The solution was then stirred at 85°C under argon for 18h. The reaction solution was then poured into water (300ml) and extracted with dichloromethane (2 x 200ml). The organic solution was dried ($MgSO_4$) and the solvent removed *in vacuo*. Chromatography (silica gel, diethyl ether/petroleum ether mixtures) afforded the title compound (3.3g).
Mass Spectrum (API$^+$): Found 215 (MH^+). $C_{14}H_{18}N_2$ requires 214.

Description 33: (RS)- 2-(1-Benzylpiperidin-2-ylmethyl)-[1,2,4]-triazolo[1,5-a]pyridine
(RS)-1-Benzyl-2-cyanomethylpiperidine, D32 (1.0g) was dissolved in dry tetrahydrofuran (10ml) containing ethanol (0.28ml). The reaction solution was then cooled to ice bath temperature and hydrogen chloride gas was bubbled through the solution for 1h. The solution was then stirred at room temperature for 16h. The resulting solution was diluted with tetrahydrofuran (30ml) and dichloromethane (30ml) and 1-aminopyridinium iodide (1.0g), followed by excess potassium carbonate and ethanol (30ml) was added. The reaction mixture was then stirred at room temperature under argon for 24h. The mixture was then filtered and the solvent removed *in vacuo*. The residue was chromatographed (silica gel, 80-20 diethyl ether-petroleum ether then 9-1 dichloromethane-methanol) to afford the title compound.
Mass Spectrum (API$^+$): Found 307 (MH^+). $C_{14}H_{18}N_2$ requires 306.

Description 34: (RS)-2-Piperidin-2-ylmethyl-5,6,7,8-tetrahydro-[1,2,4]-triazolo[1,5-a]pyridine and 2-Piperidin-2-ylmethyl-[1,2,4]-triazolo[1,5-a]pyridine
(RS)-2-(1-Benzylpiperidin-2-ylmethyl)-[1,2,4]-triazolo[1,5-a]pyridine, D33 (0.200g) was dissolved in ethanol (25ml). Palladium hydroxide (0.100g), followed by platinum IV sulphide (0.020g) were added and the reaction mixture hydrogenated at 50 psi and 50 °C for 16 h. The suspension was evaporated to yield a mixture of the title compounds (0.180g).

Description 35: (RS)-2-[(Methoxy-methyl-carbamoyl)-methyl]-piperidine-1-carboxylic acid *tert*-butyl ester

A solution of 2-carboxymethyl-piperidine-1-carboxylic acid *tert*-butyl ester (Beckett et al, J.Med.Chem., 563,1969) (2.29g, 10mmol) in DMF (20ml) was treated sequentially with *N,N*-diisopropylethylamine (4.0ml), HATU (3.8g, 10mmol) and *O,N*-dimethyl-hydroxylamine.HCl (0.98g, 10mmol). The reaction mixture was stirred under argon at room temperature for 16h. The volatiles were removed *in vacuo* and the residue was chromatographed (silica gel, diethyl ether) to afford the title compound as a white solid (2.60g, 90%).
Mass Spectrum (API$^+$):Found 187 (MH^+ - ^{t}BOC). $C_{14}H_{26}N_2O_4$ requires 286.

Description 36: (RS)-2(2-Benzofuran-2-yl-2-oxo-ethyl)-piperidine-1-carboxylic acid *tert*-butyl ester

To a solution of benzofuran (0.95g, 8.0mmol) in THF (40 ml), under argon at -40°C was added *n*-butyllithium (2.5M in hexanes) (4.00ml, 10.0mmol) over 5 min. The resultant mixture was stirred for 15 min. at -40°C then (RS)-2-[(methoxy-methyl-carbamoyl)-methyl]-piperidine-1-carboxylic acid *tert*-butyl ester, D35 (2.30g, 8.0mmol) in THF (10ml) was added over 1 min. and the resultant solution stirred for 20 min. at -40°C. The mixture was poured into saturated ammonium chloride (20 ml) and extracted with ethyl acetate (3X). The combined organics were dried ($MgSO_4$) and the solvent removed *in vacuo*. The resultant residue was chromatographed (silica gel, dichloromethane) to afford the title compound (2.2g, 84%).
^{1}H NMR δ: 1.35 (9H, s), 1.44 (1H, m), 1.65 (5H, m), 2.94 (1H, dt, J = 3 and 13Hz), 3.17 (2H, m), 4.05 (1H, broad d), 4.89 (1H, m), 7.31 (1H, t, J = 8Hz), 7.48 (1H, m), 7.57 (2H, m), 7.72 (1H, d, J = 8Hz).

Description 37: (RS)-1-Benzofuran-2-yl-2-piperidin-2-yl-ethanone

A stirring solution of (RS)-2(2-benzofuran-2-yl-2-oxo-ethyl)-piperidine-1-carboxylic acid *tert*-butyl ester, D36 (1.68g, 4.9mmol) in dichloromethane (20ml) was treated with trifluoroacetic acid (5ml). The mixture was stirred at 50°C for 1h, cooled and the volatiles removed *in vacuo*. The residue was dissolved in dichloromethane and washed with saturated sodium bicarbonate , dried ($MgSO_4$) and the solvent removed *in vacuo* to afford the title compound (1.20g, 99%).
Mass Spectrum (API$^+$):Found 244 (MH^+). $C_{15}H_{17}NO_2$ requires 243.

Description 38: (RS)-1-Benzofuran-2-yl-2-(1-{1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-piperidin-2-yl)-ethanone

The title compound was prepared from 5-(4-fluoro-phenyl)-2-methyl-thiazole-4-carboxylic acid and (RS)-1-benzofuran-2-yl-2-piperidin-2-yl-ethanone, D37 according to a procedure similar to that for Description 35.
Mass Spectrum (API$^+$): Found 463 (MH^+). $C_{26}H_{23}FN_2O_3S$ requires 462.

Description 39: (RS)-4-Bromo-2-piperidin-2-ylmethyl-1H-benzimidazole

The title compound was prepared using the method of Description 18 from 3-bromobenzene-1,2-diamine (0.50g, 2.7mmol) and 2-carboxymethyl-piperidine-1-carboxylic acid *tert*-butyl ester (0.65g, 2.7mmol) , as a pale brown amorphous solid (0.70g, 88%)
Mass spectrum (Electrospray LC/MS): Found M-H 292. $C_{13}H_{16}{}^{79}BrN_3$ requires 293.

Description 40: (RS)-1-(2-Benzofuran-2-ylmethyl-piperidin-1-yl)-2,2,2-trifluoro-ethanone
To (RS)-2-(2-Benzofuranylmethyl)piperidine, D3 (500mg, 2.3mmol) in dichloromethane containing triethylamine (0.35ml, 2.5mmol) at 0°C under argon was added trifluoroacetic anhydride (0.36ml, 2.5mmol) in dichloromethane (3ml) over 5-10 min. The reaction was stirred at room temperature for 64h, diluted with dichloromethane and washed sequentially with water and saturated sodium hydrogen carbonate, dried (Na_2SO_4) and the solvent removed *in vacuo*. Chromatography (silica gel) afforded the title compound as a solid (740mg, 99%).
^{1}H NMR δ: 1.50-1.90 (6H, m), 2.90-3.20 (2H, m), 3.27-3.35 (1H, m), 3.85-3.89 (0.66H, m), 4.51-4.54 (0.66H, m), 5.09-5-14 (0.66H, m), 6.48 and 6.50 (1H, s), 7.15-7.25 (2H, m), 7.39-7.45 (1H, m), 7.45-7.50 (1H, m).

Description 41: (RS)-1-(2-(3-Bromo-benzofuran-2-ylmethyl-piperidin-1-yl)-2,2,2-trifluoro-ethanone
To a solution of (RS)-1-(2-benzofuran-2-ylmethyl-piperidin-1-yl)-2,2,2-trifluoro-ethanone, D40 (700mg, 2.2mmol) in diethyl ether (10ml) at -12°C under argon was added a solution of bromine (360mg, 2.2mmol) in dichloromethane (4ml) drop-wise over 0.3h. The reaction mixture was allowed to reach room temperature and after 1h the volatiles were removed *in vacuo*. Re-evaporation from dichloromethane (3X) afforded the title compound as a solid (840mg, 96%).
Mass spectrum (Electrospray LC/MS): Found 310 (MH^+-Br). $C_{16}H_{15}{}^{79}BrF_3NO_2$ requires 389.

Description 42: (RS)-2-(1-(2,2,2-Trifluoro-ethanoyl)-piperidin-2-yl-methyl)-benzofuran-3-carbonitrile
To a solution of (RS)-1-(2-(3-bromo-benzofuran-2-ylmethyl-piperidin-1-yl)-2,2,2-trifluoro-ethanone, D41 (840mg, 2.1mmol) in N-methylpyrrolidinone (15ml) was added copper(I)cyanide (387mg, 4.2mmol) and the mixture refluxed for 4.5h. The reaction mixture was cooled and diluted with water (100ml), 0.880 ammonia (3ml) and ethyl acetate (3X). The combined extracts were dried (Na_2SO_4) and the solvent removed *in vacuo*. The residual oil was redissolved in ethyl acetate (75ml)and washed with water (4X), brine, dried (Na_2SO_4) and the solvent removed *in vacuo*. Chromatography (silica gel) afforded the title compound as a solid.
Mass spectrum (Electrospray LC/MS): Found 337 (MH^+). $C_{17}H_{15}F_3N_2O_2$ requires 336.

Description 43: (RS)-Morpholin-3-yl-acetic acid ethyl ester
N-chloromorpholine (24g) in diethyl ether (20ml) was added drop-wise over 2.5h to a vigorously stirred solution of potassium hydroxide (22.1g, 0.37mol) in ethanol (130ml) at 90°C. Heating was continued at 80°C for 2h. After standing at room temperature for 48h the mixture was filtered to remove the inorganics and the solvent removed from the filtrate *in vacuo*. The residue was partitioned between diethyl ether and brine, dried (Na_2SO_4) and the solvent removed *in vacuo*. The resulting brown oil was dissolved in acetonitrile (100ml). Triethylamine (25ml) and monoethyl malonate (25g) were added and the mixture heated at 16°C for 16h. The volatiles were removed *in vacuo* and the residue partitioned between saturated aqueous potassium carbonate and diethyl ether. The organic phase was dried (Na_2SO_4) and the solvent removed *in vacuo* to afford the title compound as a brown oil (3.5g).
Mass Spectrum (API^+):Found 174 (MH^+). $C_8H_{15}NO_3$ requires 173.

Description 44: (RS)-(4-{1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-morpholin-3-yl)-acetic acid ethyl ester

The title compound (1.48g, 66%)was prepared from (RS)-morpholin-3-yl-acetic acid ethyl ester, D43 (1.37g, 5.8mmol) and 5-(4-fluoro-phenyl)-2-methyl-thiazole-4-carboxylic acid (1.00g, 5.8mmol) according to a procedure similar to that described for D16.

Mass spectrum (Electrospray LC/MS): Found 393 (MH^+). $C_{19}H_{21}FN_2O_4S$ requires 392.

Description 45: (RS)-(4-{1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-morpholin-3-yl)-acetic acid

The title compound (1.33g, 99%) was prepared from (RS)-(4-{1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-morpholin-3-yl)-acetic acid ethyl ester, D44 (1.46g, 3.7mmol) according to a procedure similar to that described for D17.

Mass Spectrum (API^+):Found 363 (M-H). $C_{17}H_{17}FN_2O_4S$ requires 364.

Description 46: (RS)-2-(1-Furo[3,2-b]pyridin-2-yl)methanoyl)piperidine-1-carboxylic acid *tert*-butyl ester

The title compound was prepared using the method of Description 10 from furo[3,2-b]pyridine (1.14g, 9.6mmol) (Shiotani and Morita, *J.Het.Chem.*,23,665,1986), as a pale yellow solid (1.97g, 62%).

Mass Spectrum (API^+):Found 331(MH^+). $C_{18}H_{22}N_2O_4$ requires 330.

Description 47:(RS)-2-Piperidin-2-ylmethyl-furo[3,2-b]pyridine

The title compound was prepared using the method of Description 3 from (RS)-2-(1-furo[3,2-b]pyridin-2-yl)methanoyl)piperidine-1-carboxylic acid *tert*-butyl ester, D46 (1.95g, 5.9mmol), as a pale green gum (0.75g, 59%).

Mass Spectrum (API^+):Found 217(MH^+). $C_{13}H_{16}N_2O$ requires 216.

Description 48: (RS)-2-[1-(5-Fluorobenzofuran-2-yl)-methanoyl]-piperazine-1,4-dicarboxylic acid 1-benzyl ester 4-*tert*-butyl ester

The title compound was prepared from (RS)-2-(methoxymethylcarbamoyl)piperazine-1,4-dicarboxylic acid 1-benzyl ester 4-*tert*-butyl ester (1.25g, 3.07mmol) (WO01/00214) and 5-fluorobenzofuran (0.42g, 3.09mmol) (WO99/51575) by the method of Description 2 as a pale green gum (0.81g, 55%).

Mass spectrum (API^+): Found 505 (MNa^+). $C_{26}H_{27}FN_2O_6$ requires 482.

Description 49: (RS)-2-[1-(5-Fluoro-benzofuran-2-yl)methanoyl]-piperazine-1-carboxylic acid benzyl ester

The title compound was prepared from (RS)-2-[1-(5-fluorobenzofuran-2-yl)-methanoyl]-piperazine-1,4-dicarboxylic acid 1-benzyl ester 4-*tert*-butyl ester, D48 (0.81g, 1.68mmol) by the method of Description 52 as a pale yellow amorphous solid (0.57g, 90%).

Mass spectrum (API^+): Found 383 (MH^+). $C_{21}H_{19}FN_2O_4$ requires 382.

Description 50: (RS)-2-[1-(5-Fluoro-benzofuran-2-yl)methanoyl]-4-methyl-piperazine-1-carboxylic acid benzyl ester

97% Formic acid (0.19g, 4 mmol) was added to a stirred mixture of (RS)-2-[1-(5-fluoro-benzofuran-2-yl)methanoyl]-piperazine-1-carboxylic acid benzyl ester, D49 (0.57g, 1.5mmol) in water (5ml). Stirring was continued as a 37% formaldehyde solution in water (0.155g) was added. The resultant mixture was heated at 100°C for 3.5h, cooled, diluted with water (30ml) and basified with 2N sodium hydroxide. The mixture was extracted with ethyl acetate (2X) and the combined extracts dried (Na_2SO_4) and the solvent removed *in vacuo* to afford the title compound (0.57g, 96%).

Mass spectrum (API$^+$): Found 397 (MH^+). $C_{22}H_{21}FN_2O_4$ requires 396.

Description 51: (RS)-3-(5-Fluorobenzofuran-2-ylmethyl)-1-methylpiperazine

The title compound was prepared from (RS)-2-[1-(5-fluoro-benzofuran-2-yl)methanoyl]-4-methyl-piperazine-1-carboxylic acid benzyl ester, D50 using the method of Description 3 as a yellow gum (0.43g).

Mass spectrum (API$^+$): Found 249 (MH^+). $C_{14}H_{17}FN_2O$ require 248.

Description 52: (RS)-2-(Methoxy-methyl-carbamoyl)-piperazine-1-carboxylic acid benzyl ester

A mixture of (RS)-2-(methoxy-methyl-carbamoyl)-piperazine-1,4-dicarboxylic acid 1-benzyl ester 4-*tert*-butyl ester (WO 01/00214) (5g, 0.012 mol) in dichloromethane (100ml) and trifluoroacetic acid (20ml) was heated at 40°C for 0.5h, cooled and evaporated. The residual oil was dissolved in dichloromethane (150ml) and washed with 1M sodium hydroxide (80ml). The aqueous phase was re-extracted with dichloromethane (2X) and the combined extracts dried (Na_2SO_4) and the solvent removed *in vacuo* to give the title compound as an oil (3.6g, 100 %).

Mass spectrum (API$^+$): Found 308 (MH^+). $C_{15}H_{21}N_3O_4$ requires 307.

Description 53: (RS)-2-(Methoxy-methyl-carbamoyl)-4-methyl-piperazine-1-carboxylic acid benzyl ester

To (RS)-2-(methoxy-methyl-carbamoyl)-piperazine-1-carboxylic acid benzyl ester, D52 (3g, 10 mmol) in 1,2-dichloroethane (50ml) was added formaldehyde (0.85ml of 37% w/w solution in water, 11 mmol) and the mixture stirred at ambient temperature for 0.75 h. Sodium triacetoxyborohydride (2.55g, 12mmol) was added portionwise over 0.25h, and the resulting mixture stirred at ambient temperature for 18h. The reaction was partitioned between dichloromethane (300ml) and 1M sodium hydroxide (100ml). The aqueous was re-extracted with dichloromethane (250ml) and the combined extracts dried (Na_2SO_4) and the solvent removed *in vacuo*. The residue was chromatographed on silica gel eluting with ethyl acetate-hexane mixtures to afford the title product (3g, 96%) as a gum.

Mass spectrum (API$^+$): Found 322. $C_{16}H_{23}N_3O_4$ requires 321.

Description 54: (RS)-2-(Methoxy-methyl-carbamoyl)-4-methyl-piperazine-1-carboxylic acid dimethyl-ethyl ester

A mixture of (RS)-2-(Methoxy-methyl-carbamoyl)-4-methyl-piperazine-1-carboxylic acid benzyl ester, D53 (2.9g, 9mmol) and di-*tert*-butyl dicarbonate (2.4g, 11mmol) in ethyl acetate (180ml) was hydrogenated at NTP over 10% Pd-C (1.45g, 50% aqueous paste) for 64h. The mixture was filtered through kieselguhr, washed with ethyl acetate and the filtrate evaporated. The residue was chromatographed on silica gel eluting with ethyl acetate-methanol mixtures to afford the title product as a white solid (2.9g, 92%).
Mass spectrum (API$^+$): Found 288 (MH^+). $C_{13}H_{25}N_3O_4$ requires 287.

Description 55: (RS)-2-(1-Benzofuran-2-yl-methanoyl)-4-methyl-piperazine-1-carboxylic acid *tert*-butyl ester
The title compound (1.81g, 52%) was prepared from (RS)-2-(methoxy-methyl-carbamoyl)-4-methyl-piperazine-1-carboxylic acid dimethyl-ethyl ester, D54 (2.9g, 10.1mmol) and benzofuran (0.74g, 10.1mmol) using the method of Description 2.
Mass spectrum (API$^+$): Found 345 (MH^+). $C_{19}H_{24}N_2O_4$ requires 344.

Description 56: (RS)-3-Benzofuran-2-ylmethyl-1-methyl-piperazine
The title compound was obtained from (RS)-2-(1-benzofuran-2-yl-methanoyl)-4-methyl-piperazine-1-carboxylic acid *tert*-butyl ester, D55 (1.28g, 3.7mmol) using the method of Description 3 and was used without purification.
Mass spectrum (API$^+$): Found 231 (MH^+). $C_{14}H_{18}N_2O$ require 230.

Description 57: (RS)-1-(5-Fluoro-benzofuran-2-yl)-1-((RS)-4-methyl-piperazin-2-yl)-methanol
(RS)-2-[1-(5-Fluoro-benzofuran-2-yl)methanoyl]-4-methyl-piperazine-1-carboxylic acid benzyl ester, D50 (0.65g, 1.6mmol) in ethyl acetate (20ml) and methanol(20ml) was hydrogenated at NTP over 10% Pd-C (0.47g, 50% w/w paste in water) for 3.5h. The reaction mixture was filtered through Kieselguhr, washing well with methanol and the filtrate evaporated to afford the title product (0.41g, 90%).
^{1}H NMR δ: 2.05 and 2.70 (together 2H, m), 2.12 and 2.62 (together 2H, m), 2.24 (3H, s), 2.94 and 3.12 (2H, m), 3.28 (1H, m), 4.84 (1H, d, J = 6Hz), 6.69 (1H, s), 6.97 (1H, m), 7.19 (1H, dd, J = 8 and 2Hz), 7.36 (1H, dd, J = 8 and 4Hz).
Mass spectrum (API$^+$): Found 265 (MH^+). $C_{14}H_{17}N_2O_2$ require 264.

Description 58: (RS)-4-Fluoro-2-piperidin-2-ylmethyl-1*H*-benzoimidazole
(RS)-2-Carboxymethyl-piperidine-1-carboxylic acid *tert*-butyl ester (1.93g) was heated with 1,2-diamino-3-fluorobenzene (1.00g) (Kirk,K.L, J.Org. Chem.,1969, 34, 384) as described in Description 18 to afford the title compound (1.14g).
Mass Spectrum (API$^+$): Found 234(MH^+). $C_{13}H_{16}FN_3$ requires 333.

Description 59: (RS)-2-(5,6-Difluoro-1*H*-benzoimidazol-2-ylmethyl)-piperidine-1-carboxylic acid *tert*-butyl ester
A solution of (RS)-5,6-difluoro-2-piperidin-2-ylmethyl-1*H*-benzoimidazole, D18 (1.5g) in dichloromethane was treated with triethylamine (0.98ml), then di-*tert*-butyl dicarbonate (1.3g).

After stirring for 18h at room temperature under argon the mixture was diluted with dichloromethane then washed with HCl (2M). The aqueous phase was basified with solid K_2CO_3 and extracted with dichloromethane. The organic phase was washed with aqueous $NaHCO_3$, brine and dried ($MgSO_4$). The solvent was removed *in vacuo* to afford the title compound (2g).
Mass Spectrum (API$^+$): Found 352 (MH^+). $C_{18}H_{23}F_2N_3O_2$ requires 351.

Description 60: (RS)-2-(5,6-Difluoro-1-methyl-1*H*-benzoimidazol-2-ylmethyl)-piperidine-1-carboxylic acid *tert*-butyl ester

To a stirred suspension of sodium hydride (0.46g, 60% dispersion in mineral oil) in dimethylformamide (30ml) at 0°C, under argon, was added (RS)-2-(5,6-difluoro-1*H*-benzoimidazol-2-ylmethyl)-piperidine-1-carboxylic acid *tert*-butyl ester, D59 (2g) and the reaction mixture stirred for a further 30min. before the addition of iodomethane (0.78ml). The reaction mixture was then stirred at room temperature for 18h, a further equivalent of iodomethane (0.35ml) was added and stirring continued for 24h. Further portions of sodium hydride (0.23g, 60% dispersion in mineral oil) and iodomethane (0.35ml) were added and the reaction stirred for an additional 24h. After diluting with water, the aqueous layer was extracted with diethyl ether (3X). The combined organics were dried ($MgSO_4$) and solvent removed *in vacuo* to afford the title compound (0.5g).
Mass Spectrum (Electrospray LC/MS): Found 266 (MH^+-^{t}BOC). $C_{19}H_{25}F_2N_3O_2$ requires 365.

Description 61:(RS)-5,6-Difluoro-1-methyl-2-piperidin-2-ylmethyl-1*H*-benzoimidazole

(RS)-2-(5,6-Difluoro-1-methyl-1*H*-benzoimidazol-2-ylmethyl)-piperidine-1-carboxylic acid *tert*-butyl ester, D60 (0.5g) was treated with trifluoroacetic acid (5ml) as described for Description 6 to afford the title compound (0.363g)
Mass spectrum (Electrospray): Found 266 (MH^+). $C_{14}H_{17}F_2N_3$ requires 265.

Description 62: (RS)-2-[1-(5-Chloro-benzofuran-2-yl)-methanoyl]-4-methyl-piperazine-1-carboxylic acid *tert*-butyl ester

The title compound (0.98g) was prepared from (RS)-2-(methoxy-methyl-carbamoyl)-4-methyl-piperazine-1-carboxylic acid dimethyl-ethyl ester, D54 (1.60g) and 5-chloro-benzofuran (0.86g, FP1.537.206) using the method of Description 2.
Mass Spectrum (Electrospray LC/MS): Found 279 (MH^+-^{t}BOC). $C_{19}H_{23}{}^{35}ClN_2O_4$ requires 378.

Description 63: 3-(5-Chloro-benzofuran-2-ylmethyl)-1-methyl-piperazine

The title compound (0.61g) was prepared from (RS)-2-[1-(5-chloro-benzofuran-2-yl)-methanoyl]-4-methyl-piperazine-1-carboxylic acid *tert*-butyl ester, D62 (0.98g) using the method of Description 3 and used without purification.
Mass Spectrum (Electrospray LC/MS):Found 265 (MH^+). $C_{14}H_{17}{}^{35}ClN_2O$ requires 264.

Description 64: (RS)-2-[1-(5,7-Dichloro-benzofuran-2-yl)-methanoyl]-4-methyl-piperazine-1-carboxylic acid *tert*-butyl ester

The title compound (0.94g) was prepared from (RS)-2-(methoxy-methyl-carbamoyl)-4-methyl-piperazine-1-carboxylic acid dimethyl-ethyl ester, D54 (1.00g) and 5,7-dichloro-benzofuran (0.65g, FP1.537.206) using the method of Description 2.

Mass Spectrum (Electrospray LC/MS): Found 413 (MH^+). $C_{19}H_{22}{}^{35}Cl_2N_2O_4$ requires 412.

Description 65: (RS)-3-(5,7-Dichloro-benzofuran-2-ylmethyl)-1-methyl-piperazine

The title compound (0.53g) was prepared from (RS)-2-[1-(5,7-dichloro-benzofuran-2-yl)-methanoyl]-4-methyl-piperazine-1-carboxylic acid tert-butyl ester, D64 (0.94g) using the method of Description 3 and used without purification.

Mass Spectrum (API$^+$LC/MS): Found 299 (MH^+). $C_{14}H_{16}{}^{35}Cl_2N_2O$ requires 298.

Description 66: 1-(2-Trimethylsilanyl-ethoxymethyl)-1*H*-indole

A stirring, ice-cooled solution of indole (5.86g, 50mmol) in DMF (130ml) under argon was treated with sodium hydride (3.3g, 60% dispersion on mineral oil, 80mmol) and the reaction mixture then stirred at room temperature for 45min. After cooling to 0°C 2,2-(trimethylsilyl)ethoxymethyl chloride (12.5g, 75mmol) was added dropwise. The reaction mixture was then stirred at room temperature for 4h. The DMF was removed *in vacuo*, the residue was poured into water and the product was extracted with diethyl ether. The combined organics were washed with brine, dried (Na_2SO_4) and the solvent removed *in vacuo*. Chromatography (silica gel, 0-20% diethyl ether-40-60 pet.ether) afforded the title compound (12.2g, 100%).

^{1}HNMR δ: 0.00 (9H, s), 0.96 (2H, t, J = 8Hz), 3.53 (2H, t, J = 8Hz), 5.55 (2H, s), 6.59 (1H, m), 7.20 (2H, m), 7.30 (1H, m with $CHCl_3$), 7.55 (1H, dd, J = 1 and 8Hz), 7.70 (1H, dd, J = 1 and 8Hz).

Description 67: (RS)-2-{1-[1-(2-Trimethylsilanyl-ethoxymethyl)-1*H*-indol-2-yl]-methanoyl}-piperidine-1-carboxylic acid *tert*-butyl ester

A stirring, ice-cooled solution of 1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-indole, D66 (742mg, 3mmol) in DME (5ml) was treated drop-wise with n-butyl lithium (2.2ml, 1.6M in hexanes, 3.5mmol). The resulting green solution was stirred at 0-5°C for 15min. then was treated with (RS)-1-(*tert*-butyloxycarbonyl)-2-(N-methoxy-N-methylcarbamoyl)-piperidine, D1(952mg, 3.5mmol) in DME (2.5ml). After stirring at this temperature for a further 45 min. saturated aqueous NH_4Cl was added (10ml) and the product was extracted with diethyl ether. The organics were combined, the solvent removed *in vacuo* and the residue chromatographed (silica gel, 10% diethyl ether-pentane) to afford the title compound as a colourless oil (510mg, 37%).

Mass Spectrum (API$^+$): Found 359 (MH^+-^{t}BOC). $C_{25}H_{38}N_2O_4Si$ requires 458.

Description 68: (RS)- 2-Piperidin-2-ylmethyl-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-indole

The title compound (1.1g) was prepared from (RS)-2-{1-[1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-indol-2-yl]-methanoyl}-piperidine-1-carboxylic acid *tert*-butyl ester, D67 (1.9g) according to a procedure similar to that for Description 3 and used without purification.

Description 69 : (RS)- 2-[1-(5-Bromo-benzofuran-2-yl)-methanoyl]-piperidine-1-carboxylic acid *tert*-butyl ester

The title compound (0.96g) was prepared from 5-bromo-benzofuran (3.6g, prepared according to procedures similar to those described in Synth.Commun.,

257, (1989)) and (RS)-1-(tert-butyloxycarbonyl)-2-(N-methoxy-N-methylcarbamoyl)-piperidine, D1 (4.9g) according to a procedure similar to that for Description 2.
Mass Spectrum (API$^+$): Found 308 (MH^+-^{t}BOC). $C_{19}H_{22}{}^{79}BrNO_4$ requires 407.

Description 70:(RS)-2-(5-Bromo-benzofuran-2-ylmethyl)-piperidine
The title compound (0.53g) was prepared from (RS)- 2-[1-(5-bromo-benzofuran-2-yl)-methanoyl]-piperidine-1-carboxylic acid *tert*-butyl ester, D69 (1.00g)
according to a procedure similar to that for Description 3 and used without purification.
Mass Spectrum (API$^+$): Found 294 (MH^+). $C_{14}H_{16}{}^{79}BrNO$ requires 293.

Description 71: (RS)- 2-[1-(4-Bromo-benzofuran-2-yl)-methanoyl]-piperidine-1-carboxylic acid *tert*-butyl ester
The title compound (1.45g) was prepared from 4-bromo-benzofuran (3.65g, WO0109111) and (RS)-1-(*tert*-butyloxycarbonyl)-2-(N-methoxy-N-methylcarbamoyl)-piperidine, D1 (5.17g) according to a procedure similar to that for Description 2.
Mass Spectrum (API$^+$): Found 308 (MH^+-^{t}BOC). $C_{19}H_{22}{}^{79}BrNO_4$ requires 407.

Description 72: (RS)-2-(4-Bromo-benzofuran-2-ylmethyl)-piperidine
The title compound (0.90g) was prepared from (RS)- 2-[1-(4-bromo-benzofuran-2-yl)-methanoyl]-piperidine-1-carboxylic acid *tert*-butyl ester, D71 (1.40g)
according to a procedure similar to that for Description 3 and used without purification.

Description 73:(RS)- 2-[1-(3-Methyl-benzofuran-2-yl)-methanoyl]-piperidine-1-carboxylic acid *tert*-butyl ester
The title compound (300mg) was prepared from 3-methyl-benzofuran (390mg) and (RS)-1-(*tert*-butyloxycarbonyl)-2-(N-methoxy-N-methylcarbamoyl)-piperidine, D1 (820mg) according to a procedure similar to that for Description 2.
Mass Spectrum (API$^+$): Found 244 (MH^+-^{t}BOC). $C_{20}H_{25}NO_4$ requires 343.

Description 74: (RS)-2-(3-Methyl-benzofuran-2-ylmethyl)-piperidine
The title compound (184mg) was prepared from (RS)- 2-[1-(3-methyl-benzofuran-2-yl)-methanoyl]-piperidine-1-carboxylic acid *tert*-butyl ester, D73 (300mg)
according to a procedure similar to that for Description 3 and used without purification.

Description 75: 2-[1-(4-Fluoro-benzofuran-2-yl)-methanoyl]-piperidine-1-carboxylic acid-*tert*-butyl ester
The title compound (500mg) was prepared from 4-fluoro-benzofuran (450mg) and (RS)-1-(*tert*-butyloxycarbonyl)-2-(N-methoxy-N-methylcarbamoyl)-piperidine, D1 (900mg) according to a procedure similar to that for Description 2.
Mass Spectrum (API$^+$): Found 248 (MH^+-^{t}BOC). $C_{19}H_{22}FNO_4$ requires 347.

Description 76: (RS)- 2-(4-Fluoro-benzofuran-2-ylmethyl)-piperidine
The title compound (310mg) was prepared from (RS)- 2-[1-(4-fluoro-benzofuran-2-yl)-methanoyl]-piperidine-1-carboxylic acid *tert*-butyl ester, D75 (500mg)

according to a procedure similar to that for Description 3 and used without purification.

Description 77: (RS)- 2-[1-(4,6-Dichloro-benzofuran-2-yl)-methanoyl]-4-methyl-piperazine-1-carboxylic acid *tert*-butyl ester

The title compound (566mg) was prepared from 4,6-dichloro-benzofuran (390mg) and (RS)-1-(*tert*-butyloxycarbonyl)-2-(N-methoxy-N-methylcarbamoyl)-piperidine, D1 (600mg) according to a procedure similar to that for Description 2.

Description 78: (RS)- 3-(4,6-Dichloro-benzofuran-2-ylmethyl)-1-methyl-piperazine

The title compound (527mg) was prepared from (RS)- 2-[1-(4,6-dichloro-benzofuran-2-yl)-methanoyl]-4-methyl-piperazine-1-carboxylic acid *tert*-butyl ester, D77 (900mg) according to a procedure similar to that for Description 3 and used without purification.
Mass Spectrum (API$^+$): Found 299 (MH^+). $C_{14}H_{16}{}^{35}Cl_2N_2O$ requires 298.

Description 79: (RS)- 2-(Methoxy-methyl-carbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester

The title compound was prepared from (RS)-pyrrolidine-1,2-dicarboxylic acid 1- *tert* -butyl ester (14.8g) and N,O-dimethylhydroxylamine.HCl (7.37g) according to a procedure similar to that for Example 4.
Mass Spectrum (Electrospray LC/MS): Found 159 (MH^+-^{t}BOC). $C_{12}H_{22}N_2O_4$ requires 258.

Description 80: (RS)- 2-(1-Benzofuran-2-yl-methanoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester

The title compound (2.7g) was prepared from benzofuran (2.29g) and (RS)- 2-(methoxy-methyl-carbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester, D79 (5.00g) according to a procedure similar to that for Description 2.
Mass Spectrum (API$^+$): Found 216 (MH^+-^{t}BOC). $C_{18}H_{21}NO_4$ requires 315.

Description 81: (RS)- 2-Benzofuran-2-ylmethyl-pyrrolidine

The title compound (0.57g) was prepared from (RS)- 2-(1-benzofuran-2-yl-methanoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester, D80 (1.00g) according to a procedure similar to that for Description 3 and used without purification.

Description 82: (RS)-2-(1-Benzo[b]thiophen-2-yl-methanoyl)-piperidine-1-carboxylic acid *tert*-butyl ester

The title compound (1.60g) was prepared from benzo[b]thiophene(0.80g) and (RS)-1-(*tert*-butyloxycarbonyl)-2-(N-methoxy-N-methylcarbamoyl)-piperidine, D1 (1.62g) according to a procedure similar to that for Description 2.

Description 83: (RS)- 2-Benzo[b]thiophen-2-ylmethyl-piperidine

The title compound (410mg) was prepared from (RS)-2-(1-benzo[b]thiophen-2-yl-methanoyl)-piperidine-1-carboxylic acid *tert*-butyl ester, D82 (666mg)
according to a procedure similar to that for Description 3 and used without purification.

Example 1: (RS)-2-(2-Benzofuranylmethyl)-1-((5-(4-fluorophenyl)-2-methyl-thiazol-4-yl)-carbonyl)-piperidine

5-(4-(Fluorophenyl)-2-methyl-thiazole-4-carbonyl chloride (136 mg, 0.53 mmol) in dichloromethane (1 ml) was added to a solution of (RS)-2-(2-benzofuranylmethyl)piperidine (104 mg, 0.48 mmol) and triethylamine (0.20 ml, 1.45 mmol) in dichloromethane (4 ml) and the mixture shaken at ambient temperature for 30 min. The resultant was washed with saturated aqueous sodium hydrogen carbonate (8 ml). The organic layer was applied directly onto a pre-packed silica gel column and chromatographed eluting with ethyl acetate hexane mixtures to give the title compound (50 mg, 24 %) as an off-white solid.

Mass spectrum (API^+): found 435 (MH^+): $C_{25}H_{23}FN_2O_2S$ requires 434.

Example 2: (RS)-1-(2-Benzooxazol-2-ylmethyl-piperidin-1-yl)-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone .

5-(4-Fluoro-phenyl)-2-methyl-thiazole-4-carboxylic acid (0.05g) in dimethylformamide (2.5ml) was treated sequentially with diisopropylethylamine (0.12ml), [O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate] (0.08g) and the amine of Description 6 (0.047g) in dimethylformaide (2.5ml). The mixture was stirred for 16h, diluted with ethyl acetate and the organic phase washed with water, dried (MgSO4) and solvent removed at reduced pressure. The residue was chromatographed (silica gel, 0 → 30% ethyl acetate:pentane) to give the title compound (0.06g)

Mass spectrum (API^+): found 436 (MH^+): $C_{24}H_{22}FN_3O_2S$ requires 435.

Example 3: (RS)-1-(2-Benzooxazol-2-ylmethyl-piperidin-1-yl)-1-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone

The title compound (0.02g) was prepared from the amine of Description 6 (0.047g) and 2-(3-methyl-[1,2,4]oxadiazol-5-yl)-benzoic acid (0.045g) according to the method of Example 2.

Mass spectrum (API^+): found 403 (MH^+): $C_{23}H_{22}N_4O_3$ requires 402.

Example 4: (RS)-1-(2-Benzofuran-2-ylmethyl-piperidin-1-yl)-1-[4-(4-fluoro-phenyl)-1-methyl-1-*H*-pyrazol-3-yl]-methane

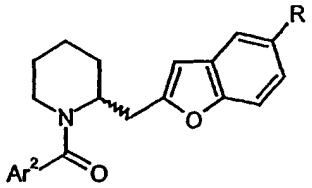
A mixture of (RS)-2-(2-benzofuranylmethyl)piperidine, D3 (0.108g, 0.5mmol), 4-(4-fluoro-phenyl)-1-methyl-1*H*-pyrazole-3-carboxylic acid (0.11g, 0.5mmol), EDC.HCl(0.106g, 0.55 mmol) and 1-hydroxybenzotriazole (0.01g, 0.07mmol) in dichloromethane (4ml) was shaken for 20h. The resultant was washed with saturated aqueous sodium bicarbonate (8ml) and the organic layer was added directly onto a dry 10g prepacked silica gel cartridge. Elution with 10-100% ethyl acetate in hexane gradient then 1-20% methanol in ethyl acetate gradient afforded the title compound as a colourless amorphous solid (0.059g, 28%).

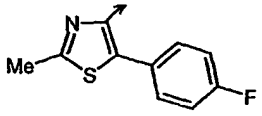
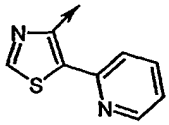
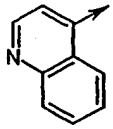
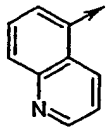
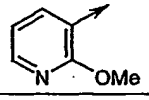
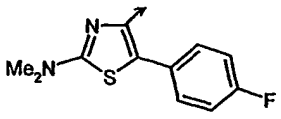
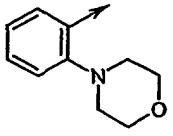
^1H NMR ($CDCl_3$) δ: 1.05 - 1.30 (1H, m), 1.35 - 1.80 (5H, m), 2.80 - 3.20 (3H, m), 3.53 (0.55 H, broad m), 3.81 and 3.93 (3H, 2 x s), 4.13 (0.45 H, broad m), 4.74 (0.45 H, broad m), 5.41 (0.55 H, broad m), 6.26 and 6.60 (1H, 2 x s), 6.85 and 6.95 (2H, 2 x t, J = 8.6 Hz), 7.10 - 7.55 (7H, m).

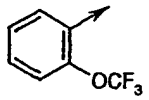
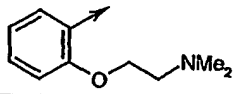
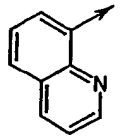
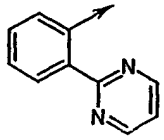
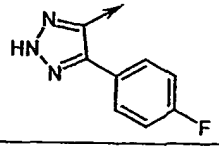
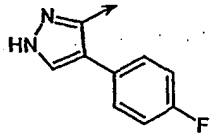
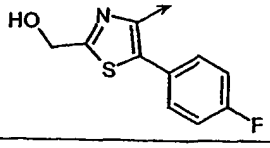
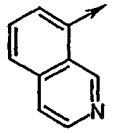
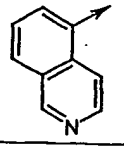
Mass spectrum (Electrospray LC/MS): Found 418 (MH^+). $C_{25}H_{24}FN_3O_2$ requires 417.

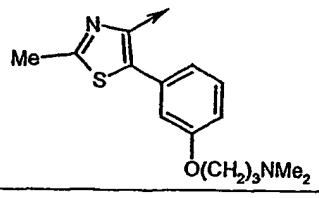
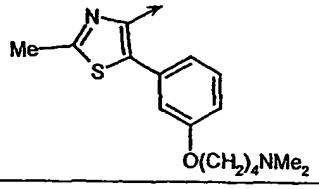
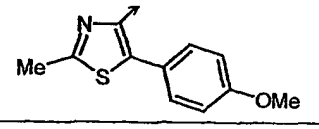
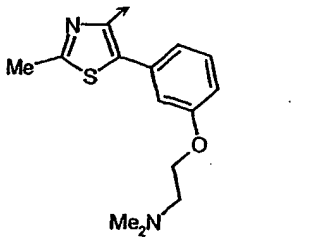
The compounds of Examples 5-22 and 90-91 in Table 1 were prepared from the appropriate amine and acid using similar procedures to that described in Example 4. The compound of Example 13 was prepared as the hydrochloride salts.

Table 1



Example	Ar^2	R	Mass Spectrum (Electrospray LC/MS)
5		F	Found MH^+453. $C_{25}H_{22}F_2N_2O_2S$ requires 452
6		F	Found MH^+422. $C_{23}H_{20}FN_3O_2S$ requires 421
7		F	Found MH^+389. $C_{24}H_{21}FN_2O_2$ requires 388
8		F	Found MH^+389. $C_{24}H_{21}FN_2O_2$ requires 388
9		F	Found MH^+369. $C_{21}H_{21}FN_2O_3$ requires 368.
10		F	Found MH^+482. $C_{26}H_{25}F_2N_3O_2S$ requires 481.
11		F	Found MH^+423. $C_{25}H_{27}FN_2O_3$ requires 422.

Example	Ar^2	R	Mass Spectrum (Electrospray LC/MS)
12		F	Found MH^+422. $C_{22}H_{19}F_4NO_3$ requires 421.
13		H	Found MH^+407. $C_{25}H_{30}N_2O_3$ requires 406
14		H	Found MH^+371. $C_{24}H_{22}N_2O_2$ requires 370.
15		H	Found MH^+398. $C_{25}H_{23}N_3O_2$ requires 397.
16		H	Found MH^+405. $C_{23}H_{21}FN_4O_2$ requires 404.
17		H	Found MH^+404. $C_{24}H_{22}FN_3O_2$ requires 403.
18		H	Found MH^+451. $C_{25}H_{23}FN_2O_3S$ requires 450.
19		H	Found MH^+371. $C_{24}H_{22}N_2O_3$ requires 370
20		H	Found MH^+371. $C_{24}H_{22}N_2O_2$ requires 370.

Example	Ar^2	R	Mass Spectrum (Electrospray LC/MS)
21		H	Found MH^+518. $C_{30}H_{35}N_3O_3S$ requires 517.
22		H	Found MH^+532. $C_{31}H_{37}N_3O_3S$ requires 531.
90		H	Found MH^+447. $C_{26}H_{26}N_2O_3S$ requires 446. (API LC/MS)
91		H	Found MH^+ 504. $C_{29}H_{33}N_3O_3S$ requires 436.

Example 23: (RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-(2-furo[2,3-*b*]pyridin-2-ylmethyl-piperidin-1-yl)-methanone

The title compound was prepared, using the method of Example 4, from 5-(4-fluoro-phenyl)-2-methyl-thiazole-4-carboxylic acid (0.171g, 0.72 mmol) and (RS)-2-piperidin-2-ylmethyl-furo[2,3-*b*]pyridine, D11 (0.13g, 0.60 mmol) as a colourless solid (0.129g, 49%).

^{1}H NMR δ: 0.90 - 1.20 (1H, m), 1.30 - 1.85 (5H, m), 2.49 and 2.70 (3H, 2 x s), 2.80 - 3.20 (3H, m), 3.40 (0.45H, m), 4.10 (0.55H, m), 4.70 (0.55, m), 5.35 (0.45H, m), 6.34 and 6.65 (1H, 2 x s), 6.92 and 7.00 (2H, 2 x t, J = 8.6 Hz), 7.15 (1H, m), 7.35 - 7.50 (2H, m), 7.80 (1H, m), 8.23 (1H, m).

Mass spectrum (Electrospray LC/MS): Found 436 (MH^+). $C_{24}H_{22}FN_3O_2S$ requires 435.

Example 24: (RS)-1-[4-(4-Fluoro-phenyl)-1-methyl-1*H*-pyrazole-3-yl]-(2-furo[2,3-*b*]pyridin-2-ylmethyl-piperidin-1-yl)methanone

The title compound was prepared using the method of Example 4, from 4-(4-(fluoro-phenyl)-1-methyl-1*H*-pyrazole-3-carboxylic acid (0.159g, 0.72mmol) and (RS)-2-piperidin-2-ylmethyl-furo[2,3-*b*]pyridine, D11(0.13g, 0.60mmol) as a colourless solid (0.12g, 48%).

Mass Spectrum (Electrospray LC/MS): Found 419 (MH^+). $C_{24}H_{23}FN_4O_2$ requires 418.

Example 25: (RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-(2-quinolin-2-ylmethyl-piperidin-1-yl)-methanone

The title compound was prepared, using the method of Example 1, from 5-(4-fluoro-phenyl)-2-methyl-thiazole-4-carbonyl chloride (0.09g, 0.35mmol) and 2-piperidin-2-ylmethyl-quinoline, D13 (0.053g, 0.23mmol) as a colourless solid (0.038g, 37%).

^{1}H NMR (DMSO-d_6) δ: 1.00-1.90 (6H, m), 2.37 and 2.66 (3H, 2 x s), 2.90-3.30 (3.5H, m), 4.15 (0.5H, m), 4.45 (0.5H, m), 5.25 (0.5H, m), 7.05 (2H, m), 7.10 - 7.85 (6H, m), 7.90 (1H, m), 8.05 - 8.30 (1H, 2 x d, J = 8.4Hz).

Mass spectrum (Electrospray LC/MS): Found 446 (MH^+). $C_{26}H_{24}FN_3OS$ requires 445.

Example 26: (RS)-1-Benzofuran-2-yl-1-(1-{1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-piperidin-2-yl)-methanone

The title compound was prepared, using the method of Example 1, from 5-(4-fluoro-phenyl)-2-methyl-thiazole-4-carbonyl chloride (0.1g, 0.39 mmol) and (RS)-1-benzofuran-2-yl-1-piperidin-2-yl-methanone, D9 (0.1g, 0.43 mmol) as a colourless solid (0.074g, 43%)

Mass spectrum (Electrospray LC/MS): Found 449 (MH^+). $C_{25}H_{21}FN_2O_3S$ requires 448.

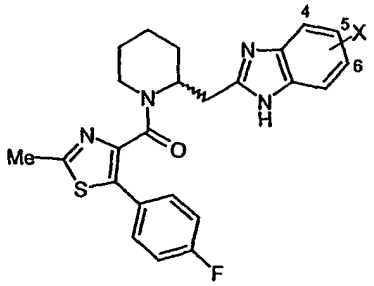
Example 27: (RS)-1-[2-(1*H*-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone

(RS)-(1-{1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-piperidin-2yl)-acetic acid, D17 (110mg, 0.3mmol) and benzene-1,2-diamine (33mg, 0.3mmol) in PPA (2g) were heated at 140°C for 3.5h. The cooled reaction mixture was poured onto a mixture of crushed ice and K_2CO_3. The basic aqueous solution was extracted with ethyl acetate (3X). The combined organics were washed with brine, dried ($MgSO_4$) and the solvent removed *in vacuo*. Chromatography (silica gel, ethyl acetate) afforded the title compound as a dark yellow gum (72mg, 52%).

Mass Spectrum (Electrospray LC/MS): Found 435 (MH^+). $C_{24}H_{23}FN_4OS$ requires 434.

The compounds of the Examples 28-34 in Table 2 below were prepared from the appropriate benzene-1,2-diamine and (RS)-(1-{1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-piperidin-2yl)-acetic acid, D17 using similar procedures to that described in Example 27.

Table 2



Example	X	Mass Spectrum (Electrospray LC/MS)

28	5-Cl	Found MH^+469. $C_{24}H_{22}{}^{35}ClFN_4OS$ requires 468.
29	5-F	Found MH^+453. $C_{24}H_{22}F_2N_4OS$ requires 452.
30	5-Cl,6-F	Found MH^+487. $C_{24}H_{21}{}^{35}ClF_2N_4OS$ requires 486.
31	4-Me	Found MH^+449. $C_{25}H_{25}FN_4OS$ requires 448.
32	4,6-di-F	Found MH^+471. $C_{24}H_{21}F_3N_4OS$ requires 470.
33	4-CH_2NMe_2	Found MH^+492. $C_{27}H_{30}FN_5OS$ requires 491.
34	5-Br	Found MH^+ 513. $C_{24}H_{22}{}^{79}BrFN_4OS$ requires 512.

Example 35: (RS)-1-[2-(5,6-Difluoro-1*H*-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone

A solution of 5-(4-fluoro-phenyl)-2-methyl-thiazole-4-carboxylic acid (700mg, 3.0 mmol), HATU (1.12g, 3.0mmol) and N,N-diisopropylethylamine (1.54ml, 9.0mmol) in DMF (20ml) was stirred at room temperature under argon for 2 min. The mixture was then treated with (RS)-5,6-difluoro-2-piperidin-2-ylmethyl-1*H*-benzoimidazole, D18 (742 mg, 3.0mmol) and stirring was continued for 16h. The solvent was removed *in vacuo* and the residue partitioned between water and ethyl acetate. The organic phase was dried (Na_2SO_4) and the solvent removed *in vacuo*. Chromatography (silica gel, 0-5% methanol-ethyl acetate) afforded the title compound as a pale yellow solid (1.35g, 97%).

Mass spectrum (Electrospray LC/MS): Found 471 (MH^+). $C_{24}H_{21}F_3N_4OS$ requires 470

^1H NMR δ: 0.80-1.90 (6H + H_2O, bm), 2.71 and 2.75(3H, 2Xs), 3.04 (IH, dt, J = 3 and 13Hz), 3.17 (0.8H, dd, J = 5 and 13Hz), 3.42-3.58 (1.8H, bm), 3.74 (0.2H, m), 4.43 (0.4H, m), 5.35 (1H, 0.8H, m), 6.75 (1.6H, t, J = 8Hz), 7.00-7.20 (3H, bm), 7.40-7.57 (1.4H, m), 11.30 and 12.38 (1H, 2Xbs).

The title compound (900mg) was dissolved in methanol and treated with 1M HCl in diethyl ether (excess). The volatiles were removed *in vacuo* and the residue was triturated with ethyl acetate to give a white solid (805mg). A sample (450mg) was crystallised form ethyl acetate to give the hydrochloride salt of the title compound as white solid (420mg).

Mass spectrum (Electrospray LC/MS) Found 471.$C_{24}H_{21}F_3N_4OS$ requires 470.

Example 36: (RS)-1-[2-(4,5-Difluoro-1*H*-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone

A solution of 5-(4-fluoro-phenyl)-2-methyl-thiazole-4-carboxylic acid (1.00g, 4.2mmol), HATU (1.60g, 4.2mmol) and N,N-diisopropylethylamine (2.00ml, 11.6mmol) in DMF (20ml) was stirred at room temperature under argon for 2 min. The mixture was then treated with (RS)-4,5-difluoro-2-piperidin-2-ylmethyl-1*H*-benzoimidazole, D21 (1.06g, 4.2mmol) and stirring was continued for

16h. The solvent was removed *in vacuo* and the residue was washed with water then was triturated with ethyl acetate to afford the title compound as an off-white solid (1.68g, 85%).
Mass spectrum (Electrospray LC/MS): Found 471 (MH^+). $C_{24}H_{21}F_3N_4OS$ requires 470.
The title compound (650mg) was dissolved in methanol and treated with 1M HCl in diethyl ether (excess). The volatiles were removed *in vacuo* and the residue was triturated with ethyl acetate to afford the hydrochloride salt of the title compound as a white solid (615mg).
Mass spectrum (Electrospray LC/MS) Found 471 (MH^+). $C_{24}H_{21}F_3N_4OS$ requires 470.

Example 37: (RS)-1-[2-(5,6-Difluoro-1*H*-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-hydroxymethyl-thiazol-4-yl]-methanone
A strirring solution of 5-(4-fluoro-phenyl)-2-hydroxymethyl-thiazole-4-carboxylic acid (632mg, 2.0mmol, 80% pure), EDC.HCl (311mg, 2.0mmol) and 1-hydroxybenzotriazole (270mg, 2.0mmol) in DMF (20ml) was treated with (RS)-5,6-difluoro-2-piperidin-2-ylmethyl-1*H*-benzoimidazole, D18 (500mg, 2.0mmol). The reaction mixture was stirred at room temperature, under argon for 16h. The DMF was removed *in vacuo* and the residue was partitioned between ethyl acetate and water. The organic phase was dried (Na_2SO_4) and the solvent removed *in vacuo*. Chromatography (silica gel, 0-10% methanol-ethyl acetate) afforded the title compound as a pale yellow solid (350mg, 36%).
Mass spectrum (Electrospray LC/MS): Found 487 (MH^+). $C_{24}H_{21}F_3N_4O_2S$ requires 486.
^1H NMR (DMSO-d_6) δ: 0.90-1.80 (6H, bm), 2.92-3.30 (3H + DMSO, bm), 4.15 (0.4H, m), 4.40-4.60 (1H, bm), 4.73 (1H, d, J = 9Hz), 5.30 (0.6H, m), 6.20 (1H, m), 7.05-7.65 (6H, bm), 12.24 and 12.56 (1H, 2Xbs).
The title compound (350mg) was dissolved in methanol and treated with 1M HCl in diethyl ether (excess). The volatiles were removed *in vacuo* and the residue was triturated with EtOAc to afford the hydrochloride salt of the title compound as a white solid (215mg).
Mass spectrum (Electrospray LC/MS) Found 487 (MH^+).$C_{24}H_{21}F_3N_4O_2S$ requires 486.

Example 38: (RS)-1-[2-(4,5-Difluoro-1*H*-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-hydroxymethyl-thiazol-4-yl]-methanone
A strirring solution of 5-(4-fluoro-phenyl)-2-hydroxymethyl-thiazole-4-carboxylic acid (320mg, 1.0mmol, 80% pure) and (RS)-4,5-difluoro-2-piperidin-2-ylmethyl-1*H*-benzoimidazole, D21 (250mg, 1.0mmol) in DMF (10ml) was treated with EDC.HCl (194mg, 1.0mmol) and 1-hydroxybenzotriazole (50mg, 0.4mmol). The reaction mixture was stirred at room temperature, under argon for 16h. The resulting solution was diluted with diethyl ether then washed with saturated aqueous $NaHCO_3$, water (3X) and brine. Drying ($MgSO_4$) and removal of the solvent *in vacuo* afforded an orange gum. Chromatography (silica gel, 0-2% methanol-dichloromethane) afforded the title compound as an orange powder (160mg, 33%).
Mass spectrum (Electrospray LC/MS) Found 487 (MH^+). $C_{24}H_{21}F_3N_4O_2S$ requires 486.
The title compound (80mg) was dissolved in methanol and treated with 1M HCl in diethyl ether (excess). The volatiles were removed *in vacuo* and the residue was triturated with diethyl ether to afford the hydrochloride salt of the title compound as a pale orange solid (65mg).
Mass spectrum (Electrospray LC/MS): Found 487 (MH^+). $C_{24}H_{21}F_3N_4O_2S$ requires 486.

Example 39: (RS)-1-[2-(5,6-Difluoro-1*H*-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[4-(4-fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanone

A solution of 4-(4-fluoro-phenyl)-1-methyl-1*H*-pyrazole-3-carboxylic acid (73mg, 0.33mmol), HATU (124mg, 0.33mmol) and *N,N*-diisopropylethylamine (0.35ml) in DMF (6ml) was stirred at room temperature under argon for 0.5h. The mixture was then treated with (RS)-5,6-difluoro-2-piperidin-2-ylmethyl-1*H*-benzoimidazole.2HCl, D20 (105mg, 0.33mmol) and stirring, under argon was continued for 16h. The reaction mixture was diluted with diethyl ether and washed with water (3X), dried ($MgSO_4$) and the solvent removed *in vacuo*. Chromatography (silica gel, ethyl acetate) afforded the title compound (88mg, 57%).

Mass spectrum (Electrospray LC/MS): Found 454 (MH^+). $C_{24}H_{22}F_3N_5O$ requires 453.

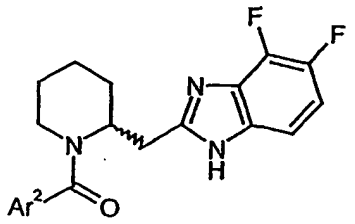
Example 40: (RS)-1-[2-(5-Methoxy-1*H*-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone

A stirring mixture of (1-{1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-piperidin-2yl)-acetic acid, D17 (150mg, 0.42mmol) and 4-methoxy-benzene-1,2-diamine (58mg, 0.42mmol) was heated at 120°C for 4h. The cooled reaction mixture was dissolved in ethyl acetate, washed with sodium hydrogen carbonate (2X) then brine. The solvent was removed *in vacuo* and the residue was chomatographed (silica gel, ethyl acetate) to afford the title compound as a brown gum (25mg, 13%).

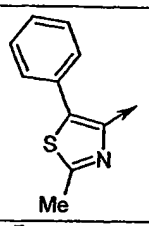
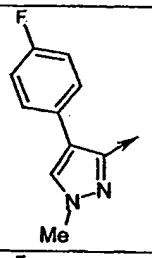
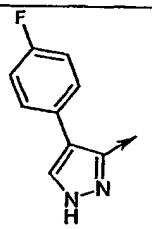
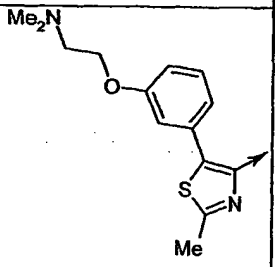
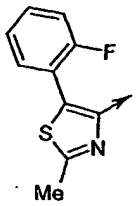
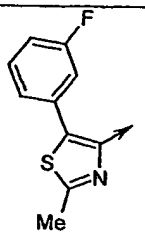
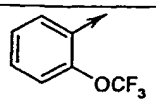
Mass spectrum (Electrospray LC/MS): Found 465 (MH^+). $C_{25}H_{25}FN_4O_2S$ requires 464.

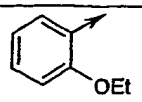
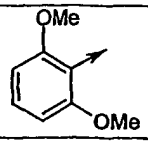
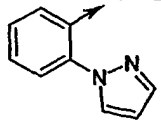
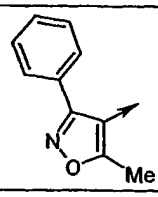
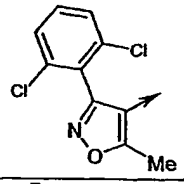
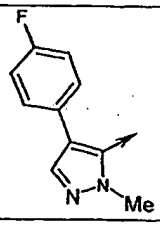
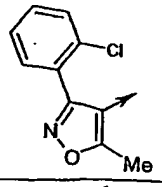
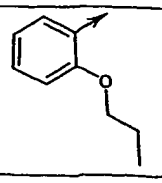
The compounds of the Examples 41-50 and 92-108 were prepared from the appropriate carboxylic acid or acid chloride and (RS)-4,5-difluoro-2-piperidin-2-ylmethyl-1*H*-benzoimidazole, D21 using a similar procedure to that described in Example 2 or a procedure similar to that described in Examples 1 or 4. The compounds of Examples 47, 48 and 49 were converted to hydrochloride salts by treatment with 1M HCl in diethyl ether. The compound of Example 96 was prepared as the trifluoroacetate salt.

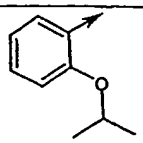
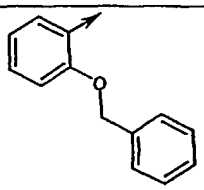
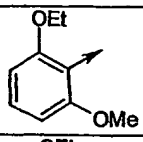
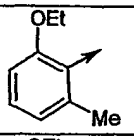
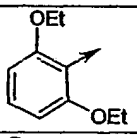
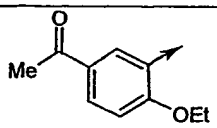
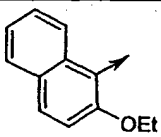
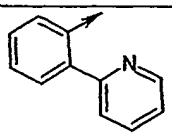
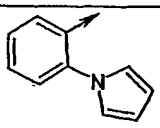
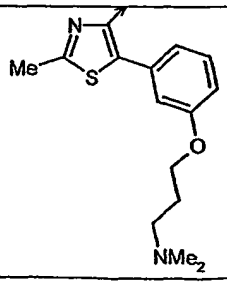
Table 3

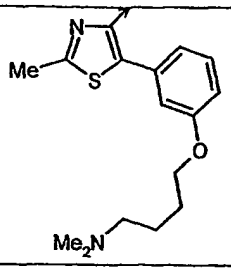


Example	Ar^2	Method	Mass Spectrum (Electrospray LC/MS)

41		E2	Found MH^+453. $C_{24}H_{22}F_2N_4OS$ requires 452.
42		E2	Found MH^+454. $C_{24}H_{22}F_3N_5O$ requires 453.
43		E2	Found MH^+440. $C_{23}H_{20}F_3N_5O$ requires 439.
44		E2	Found MH^+540. $C_{28}H_{31}F_2N_5O_2S$ requires 539.
45		E4	Found MH^+471. $C_{24}H_{21}F_3N_4OS$ requires 470.
46		E4	Found MH^+471. $C_{24}H_{21}F_3N_4OS$ requires 470.
47		E2	Found MH^+440. $C_{21}H_{18}F_5N_3O_2$ requires 439.

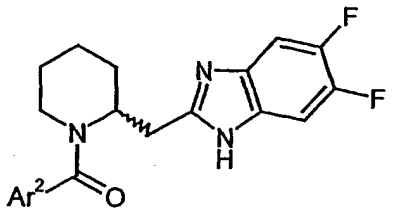
48		E2	Found MH^+ 400. $C_{22}H_{23}F_2N_3O_2$ requires 399.
49		E2	Found MH^+ 416. $C_{22}H_{23}F_2N_3O$ requires 415.
50		E2	Found MH^+ 422. $C_{23}H_{21}F_2N_5O$ requires 421.
92		E2	Found MH^+ 437. $C_{24}H_{22}F_2N_4O_2$ requires 436.
93		E2	Found MH^+ 505. $C_{24}H_{20}{}^{35}Cl_2F_2N_4O_2$ requires 504.
94		E2	Found MH^+ 454. $C_{24}H_{22}F_3N_5O$ requires 453.
95		E1	Found MH^+ 489. $C_{24}H_{20}{}^{35}ClF_3N_4O_2$ requires 488.
96		E2	Found MH^+ 471. $C_{24}H_{21}{}^{35}ClF_2N_4O_2$ requires 470.
97		E2	Found MH^+ 414. $C_{23}H_{25}F_2N_3O_2$ requires 413.

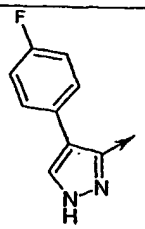
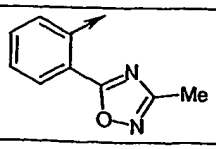
98		E2	Found MH^+ 414. $C_{23}H_{25}F_2N_3O_2$ requires 413.
99		E2	Found MH^+ 462. $C_{27}H_{25}F_2N_3O_2$ requires 461.
100		E2	Found MH^+ 430. $C_{23}H_{25}F_2N_3O_3$ requires 429.
101		E2	Found MH^+ 414. $C_{23}H_{25}F_2N_3O_2$ requires 413.
102		E2	Found MH^+ 444. $C_{24}H_{27}F_2N_3O_3$ requires 443.
103		E2	Found MH^+ 442. $C_{24}H_{25}F_2N_3O_3$ requires 441.
104		E2	Found MH^+ 450. $C_{26}H_{25}F_2N_3O_2$ requires 449.
105		E2	Found MH^+ 433. $C_{25}H_{22}F_2N_4O$ requires 432.
106		E2	Found MH^+ 421. $C_{24}H_{22}F_2N_4O$ requires 420.
107		E2	Found MH^+ 554. $C_{29}H_{33}F_2N_5O_2S$ requires 553.

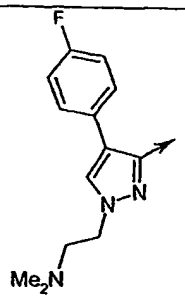
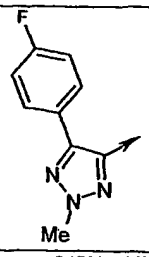
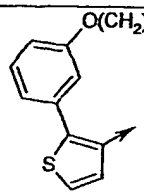
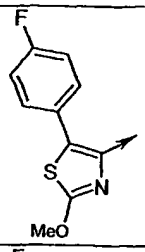
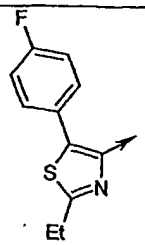
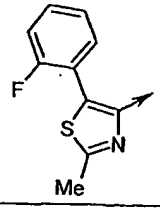
108		E2	Found MH^+ 568. $C_{30}H_{35}F_2N_5O_2S$ requires 567.

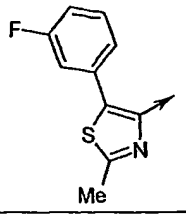
The compounds of the Examples 51-55 and 109-112 in Table 4 were prepared from the appropriate carboxylic acid and (RS)-5,6-difluoro-2-piperidin-2-ylmethyl-1*H*-benzoimidazole, D18 using a similar procedure to that described in Example 2 or Example 4 or from the appropriate acid chloride and (RS)-5,6-difluoro-2-piperidin-2-ylmethyl-1*H*-benzoimidazole, D18 using a procedure similar to that described for Example 1. The compound of Example 55 was converted to the hydrochloride salt by treatment with 1M HCl in diethyl ether. The compound of Example 109 was prepared as the trifluoroacetate salt.

Table 4



Example	Ar^2	Method	Mass Spectrum (Electrospray LC/MS)
51		E2	Found MH^+440. $C_{23}H_{20}F_3N_5O$ requires 439.
52		E2	Found MH^+438. $C_{23}H_{21}F_2N_5O_2$ requires 437

53		E2	Found MH^+511. $C_{27}H_{29}F_3N_6O$ requires 510
54		E2	Found MH^+455. $C_{23}H_{21}F_3N_6O$ requires 454
55		E1	Found MH^+539. $C_{29}H_{32}F_2N_4O_2S$ requires 538.
109		E4	Found MH^+ 487. $C_{24}H_{21}F_3N_4O_2S$ requires 486.
110		E2	Found MH^+ 485. $C_{25}H_{23}F_3N_4OS$ requires 484.
111		E4	Found MH^+ 471. $C_{24}H_{21}F_3N_4OS$ requires 470.

112		E4	Found MH^+ 471. $C_{24}H_{21}F_3N_4OS$ requires 470.

Example 56: (RS)-1-[2-(5,6-Difluoro-1-methyl-1*H*-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone

(RS)-1-[2-(5,6-Difluoro-1*H*-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone, E35 (400mg, 0.85mmol) was slowly added to an ice-cooled slurry of NaH (68mg, 60% dispersion on mineral oil, 1.7mmol) in DMF (10ml). After 0.5h iodomethane (0.90mmol) was added. The reaction mixture was stirred at room temperature, under argon for 16h. 2N HCl (9 drops) then water (100ml) were added. The aqueous phase was extracted with EtOAc(2X) and the combined organics washed with brine, dried (Na_2SO_4) and the solvent removed *in vacuo*. The residue was chromatographed (silica gel, 50-100% pentane-ethyl acetate). Residual DMF was removed by dissolving in ethyl acetate/diethyl ether and washing with water (2X). Drying (Na_2SO_4) and removal of the solvent *in vacuo* afforded the title compound as a pale yellow solid (142mg, 34%).

Mass spectrum (Electrospray LC/MS): Found 485 (MH^+). $C_{25}H_{23}F_3N_4OS$ requires 484.

Example 57: 1-[(S)-2-(1*H*-Benzoimidazol-2-ylmethyl)-pyrrolidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone The title compound was prepared from (S)-pyrrolidin-2-ylmethyl-1H-benzoimidazole, D26 and 5-(4-fluoro-phenyl)-2-methyl-thiazole-4-carboxylic acid by a procedure similar to that described for Example 2. Chromatography (silica gel, 0-8%[10% .880 NH3 in MeOH] in dichloromethane) afforded the title compound as a brown gum.

Mass spectrum (API^+): found 421 (MH^+). $C_{23}H_{21}N_4OS$ requires 420.

Example 58: 1-[(S)-2-(5,6-Difluoro-1*H*-benzoimidazol-2-ylmethyl)-pyrrolidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone

The title compound was prepared from, (S)-5,6-difluoro-pyrrolidin-2-ylmethyl-1H-benzoimidazole, D27 and 5-(4-fluoro-phenyl)-2-methyl-thiazole-4-carboxylic acid by a procedure similar to that described for Example 1. Chromatography (silica gel, 0-8%[10% .880 NH_3 in methanol] in dichloromethane) afforded the title compound as a beige solid.

Mass spectrum (API^+): found 457 (MH^+). $C_{23}H_{19}F_3N_4OS$ requires 456.

Example 59: 1-[(S)-2-(5,6-Difluoro-1*H*-benzoimidazol-2-ylmethyl)-pyrrolidin-1-yl]-1-[4-(4-fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]methanone

The title compound was prepared from, (S)-5,6-difluoro-pyrrolidin-2-ylmethyl-1H-benzoimidazole, D27 and 4-(4-fluoro-phenyl)-1-methyl-1*H*-pyrazole-3-carboxylic acid by a procedure similar to that described for Example 2. Chromatography (silica gel, 0 → 8%[10% .880 NH_3 in methanol] in dichloromethane) afforded the title compound as a beige solid.

Mass spectrum (API^+): found 440(MH^+): $C_{23}H_{20}F_3N_5O$ requires 439.

Example 60: (RS)-1-(2-Benzothiazol-2-ylmethylpiperidin-1-yl)-1-[5-(4-fluorophenyl)-2-methylthiazol-4-yl]-methanone

2-Piperidin-2-ylmethylbenzothiazole, D30 (0.135 g), HATU (0.228 g), diisopropylethylamine (0.300 ml) and 5-(4-fluorophenyl)-2-methylthiazol-4-carboxylic acid (0.144g) were dissolved in dry DMF and shaken at room temperature for 16 hours. The solvent was then evaporated and the residue partitioned between dichloromethane and brine. The organic layer was dried ($MgSO_4$), evaporated and the residue chromatographed over silica gel. Elution with diethyl ether provided the title compound as a foam (220 mg).
Mass spectrum (API^+): found 452(MH^+): $C_{24}H_{22}FN_3OS_2$ requires 451.

Example 61: (RS)-1-(2-Benzothiazol-2-ylmethylpiperidin-1-yl)-1-[4-(4-fluorophenyl)-1-methyl-1-*H*-pyrazol-3-yl]-methanone

The title compound (0.210 g) was prepared from 2-piperidin-2-ylmethyl-benzothiazole, D30 (0.135 g) and 4-(4-fluorophenyl)-1-methyl-1-*H*-pyrazol-3-carboxylic acid (0.135 g) using the procedure described in Example 60.
Mass spectrum (API^+): found 435(MH^+): $C_{24}H_{23}FN_4OS$ requires 434.

Example 62: (RS)-1-(2-Benzothiazol-2-ylmethylpiperidin-1-yl)-1-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)phenyl]-methanone

The title compound (0.170 g) was prepared from 2-piperidin-2-ylmethyl-benzothiazole, D30 (0.135 g), and 2-(3-methyl-[1,2,4]oxadiazol-5-yl)benzoic acid (0.126 g) using the procedure described in Example 60.
Mass spectrum (API^+): found 419(MH^+): $C_{23}H_{22}N_4O_2S$ requires 418.

Example 63 and Example 64: (RS)-1-[5-(4-Fluorophenyl)-2-methylthiazol-4-yl]-1-[2-(5,6,7,8-tetrahydro-[1,2,4]-triazolo[1,5-a]pyridin-2-ylmethyl)-piperidin-1-yl]-methanone and (RS)-1-[5-(4-Fluorophenyl)-2-methylthiazol-4-yl]-1-(2-[1,2,4]triazolo[1,5-a]pyridin-2-ylmethylpiperidin-1-yl)-methanone

The mixture of 2-piperidin-2-ylmethyl-5,6,7,8-tetrahydro-[1,2,4]-triazolo[1,5-a]pyridine and 2-piperidin-2-ylmethyl-[1,2,4]-triazolo[1,5-a]pyridine, D34 (0.220 g) was treated with HATU (0.380 g), *N,N*-diisopropylethylamine (1.0 ml) and 5-(4-fluorophenyl)-2-methylthiazole-4-carboxylic acid (0.240g) in dry DMF, according to the procedure described in Example 60. The crude product was chromatographed (silica gel , 4% methanol-diethyl ether) to afford 1-[5-(4-fluoro-phenyl)-2-methylthiazol-4-yl]-1-(2-[1,2,4]-triazolo[1,5-a]pyridin-2-ylmethylpiperidin-1-yl)-methanone as a colourless foam (0.070 g) (Mass spectrum (API^+): found 436(MH^+): $C_{23}H_{22}FN_5OS$ requires 435). Continued elution (10% methanol-diethyl ether) afforded 1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[2-(5,6,7,8-tetrahydro-[1,2,4]-triazolo[1,5-a]pyridin-2-ylmethyl)-piperidin-1-yl]-methanone as a colourless foam (0.230 g) (Mass spectrum (API^+): found 440(MH^+): $C_{23}H_{26}FN_5OS$ requires 439).

Example 65a and b : 1-[(RS)-2-((RS)-2-Benzofuran-2-yl-2-hydroxy-ethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone (as separate diastereoisomers)

A solution of (RS)-1-Benzofuran-2-yl-2-(1-{1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-piperidin-2-yl)-ethanone, D38 (50mg, 0.11mmol) in methanol was treated with sodium borohydride (50mg). The reaction mixture was stirred at room temperature, under argon for 16h. The volatiles were removed *in vacuo* and the residue was triturated with dichloromethane. The dichloromethane soluble material was chromatographed (silica gel, diethyl ether) to afford, separately the two diastereoisomers of the title compound.

Mass spectrum (API^+) : found 447 ($MH^+ - H_2O$): $C_{26}H_{25}FN_2O_3S$ requires 464 (first eluting diastereoisomer).

Mass spectrum (API^+): found 447 ($MH^+ - H_2O$): $C_{26}H_{25}FN_2O_3S$ requires 464 (second eluting diastereoisomer)

Example 66: (RS)-1-[2-(4-Bromo-1*H*-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluorophenyl)-2-methylthiazol-4-yl]methanone

2-Methyl-5-(4-fluorophenyl)thiazole-4-carbonyl chloride (383mg, 1.5mmol) was added portionwise over 5 min. to a stirred solution of (RS)-4-bromo-2-piperidin-2-ylmethyl-1*H*-benzoimidazole, D39 (400mg, 1.4mmol) and triethylamine (0.57ml, 5.0mmol) in dichloromethane (20ml) at room temperature. After 20h the mixture was washed with saturated sodium hydrogen carbonate. The organic layer was dried (Na_2SO_4) and the solvent removed *in vacuo*. Chromatography (silica gel , 10-100% ethyl acetate-hexane then 1-10% methanol-ethyl acetate) afforded the title compound as a pale brown amorphous solid (620mg, 89%).

Mass spectrum (Electrospray LC/MS): Found 513 (MH^+). $C_{24}H_{22}{}^{79}BrFN_4OS$ requires 512.

Example 67: (RS)-1-[2-(4-Cyano-1*H*-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluorophenyl)-2-methylthiazol-4-yl]methanone

A mixture of (RS)-1-[2-(4-bromo-1*H*-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluorophenyl)-2-methylthiazol-4-yl]methanone, E66 (216mg, 0.42mmol) and copper(I)cyanide (76mg, 0.84mmol) in N-methylpyrrolidinone (15ml) was heated at reflux for 3h. The reaction mixture was cooled, poured into water and extracted with ethyl acetate (2X). Solid sodium chloride was added to the aqueous layer which was further extracted with ethyl acetate (2X). The combined organic extracts were washed with brine, dried (Na_2SO_4) and the solvent removed *in vacuo*. The residue was Chromatograped (silica gel, 10-100% ethyl acetate-hexane then 1-20% methanol-ethyl acetate). Further purification by HPLC (Supercosil ABZ^+, 5-95% acetonitrile containing 0.1% trifluoroacetic acid-water containing 0.1% trifluoroacetic acid) afforded the title compound as a pale brown amorphous solid (5.3mg, 3%).

Mass spectrum (Electrospray LC/MS): Found 460 (MH^+). $C_{25}H_{22}FN_5OS$ requires 459.

Example 68: (RS)-1-[2-(4-Acetyl-1*H*-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluorophenyl)-2-methylthiazol-4-yl]methanone

To a deoxygenated solution of (RS)-1-[2-(4-bromo-1*H*-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluorophenyl)-2-methylthiazol-4-yl]methanone, E66 (200mg, 0.39mmol) in anhydrous 1,4-dioxane (10ml) was added tributyl(1-ethoxyvinyl)tin (155mg, 0.43mmol) and

tetrakis(triphenylphosphine)palladium(0) (30mg, 0.026mmol). The resultant mixture was refluxed under argon for 20h. Further tetrakis(triphenylphosphine)palladium(0) (60mg, 0.052mmol) was added and refluxing continued for a further 24h. On cooling, water (15ml) and 5N hydrochloric acid (10 drops) were added and the mixture stirred at room temperature for 2h. The reaction mixture was poured into water and extracted with ethyl acetate (3X). The combined organics were dried (Na_2SO_4) and the solvent removed *in vacuo*. Chromatography (silica gel, 0-100% ethyl acetate-hexane then 2-5% methanol-ethyl acetate) afforded the title compound as a pale orange solid (62mg, 33%).
Mass spectrum (Electrospray LC/MS): Found 475 (M-H). $C_{26}H_{25}FN_4O_2S$ requires 476.

Example 69: (RS)-2-(1-{1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-piperidin-2-ylmethyl)-1H-benzoimidazole-5-carbonitrile
A stirring mixture of (RS)-1-[2-(5-bromo-1H-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone, E34 (25mg, 0.44mmol) and copper(I)cyanide (79mg, 0.88mmol) in N-methylpyrrolidinone (7ml) under argon was heated at 200°C for 5h. The cooled reaction mixture was diluted with water/ethyl acetate and filtered through Kieselghur. The organic phase was washed with water (2X), brine (2X), dried ($MgSO_4$) and the solvent removed *in vacuo* . The residue was chromatograped (silica gel, 0-4% methanol (containing 10% .0.880 ammonia)- dichloromethane). Further purification by HPLC (Supercosil ABZ$^+$, 5-95% acetonitrile containing 0.1% trifluoroacetic acid-water containing 0.1% trifluoroacetic acid) afforded the title compound as a pale brown gum (2mg, 1%).
Mass spectrum (Electrospray LC/MS): Found 460 (MH^+). $C_{25}H_{22}FN_5OS$ requires 459.

Example 70: (RS)-1-[2-(5,6-Difluoro-1-propyl-1*H*-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
(RS)-1-[2-(5,6-Difluoro-1*H*-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone, E35 (150mg, 0.32mmol) was added slowly to an ice-cooled slurry of sodium hydride (26mg, 0.64mmol, 60% dispersion in mineral oil) in DMF (10ml). After stirring for a further 0.5h, 1-iodopropane (60mg, 0.35mmol) was added. The mixture was stirred at room temperature for 16h then partitioned between water and ethyl acetate. The organic phase was washed with water, brine, dried (Na_2SO_4) and the solvent removed *in vacuo*. Chromatography (silica gel, 50-100% ethyl acetate-pentane then 0-5% methanol-ethyl acetate) afforded the title compound as a white solid.
Mass spectrum (Electrospray LC/MS): Found 513 (MH^+). $C_{27}H_{27}F_3N_4OS$ requires 512.
The product was dissolved in methanol and treated with 1M HCl in diethyl ether (excess). The volatiles were removed *in vacuo* to afford the hydrochloride salt of the title compound as pale green solid (170mg).
Mass spectrum (Electrospray LC/MS): Found 513. $C_{27}H_{27}F_3N_4OS$ requires 512.

Example 71: (RS)-1-{2-[5,6-Difluoro-1-(2-methoxy-ethyl)-1*H*-benzoimidazol-2-ylmethyl]-piperidin-1-yl}-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
(RS)-1-[2-(5,6-Difluoro-1*H*-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone, E35 (300mg, 0.64mmol) was added slowly to an ice-cooled slurry of sodium hydride (51mg, 1.3mmol, 60% dispersion in mineral oil) in DMF (10ml). After

stirring for 0.5h 1-bromo-2-methoxy-ethane (139mg, 1.0mmol), *N,N*-diisopropylethylamine (0.3ml) and potassium iodide (5mg) was added. The mixture was stirred at room temperature for 0.5h then 100°C for 16h. The volatiles were removed *in vacuo* from the cooled reaction mixture. The residue was partitioned between ethyl acetate and water. The aqueous phase was extracted with ethyl acetate (2X). The combined organics were dried (Na_2SO_4) and the solvent removed *in vacuo*. The residue was triturated with ethyl acetate to afford the title compound as a solid (306mg, 65%).
Mass spectrum (Electrospray LC/MS) Found 529 (MH^+). $C_{27}H_{27}F_3N_4O_2S$ requires 528.
The product was dissolved in methanol and treated with 1M HCl in diethyl ether (excess). The volatiles were removed *in vacuo* and the residue triturated with methanol-ethyl acetate to afford the hydrochloride salt of the title compound as a white solid (66mg).
Mass spectrum (Electrospray LC/MS): Found 529 (MH^+). $C_{27}H_{27}F_3N_4O_2S$ requires 528.

Example 72: (RS)-1-{2-[1-(2-Dimethylamino-ethyl)-5,6-difluoro-1*H*-benzoimidazol-2-ylmethyl]-piperidin-1-yl}-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
The title compound was prepared from (RS)-1-[2-(5,6-difluoro-1*H*-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone, E35 (300mg) and (2-chloro-ethyl)-dimethyl-amine, according to a procedure similar to that described for Example 71 as a white solid (88mg, 26%).
Mass spectrum (Electrospray LC/MS): Found 542 (MH^+). $C_{28}H_{30}F_3N_5OS$ requires 541.
The hydrochloride salt of the title compound was prepared as described for E71
Mass spectrum (Electrospray LC/MS): Found 542 (MH^+). $C_{28}H_{30}F_3N_5OS$ requires 541.

Example 73: (RS)-1-{2-[5,6-difluoro-1-(2-hydroxy-ethyl)-1*H*-benzoimidazol-2-ylmethyl]-piperidin-1-yl}-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
(RS)-1-[2-(5,6-Difluoro-1*H*-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone, E35 (250mg, 0.53mmol) was added slowly to an ice-cooled slurry of sodium hydride (43mg, 1.1mmol, 60% dispersion in mineral oil) in DMF (10ml), under argon. After stirring for a further 0.5h, 2-bromoethanol (0.045ml, 0.64mmol) was added. The mixture was heated at 110°C for 48h, but only a minor amount of product had formed (MS). Potassium carbonate (1.00g), N,N-diisopropylethylamine (1.0ml) and a further portion of 2-bromoethanol (0.5ml) were added and heating was continued for 16h. The volatiles were removed *in vacuo* from the cooled reaction mixture. The residue was partitioned between ethyl acetate and water. The organic phase was dried (Na_2SO_4) and the solvent removed *in vacuo*.
Chromatography (silica gel, 0-5% methanol-ethyl acetate) afforded the title compound as a white solid (78mg, 29%).
Mass spectrum (Electrospray LC/MS): Found 515 (MH^+). $C_{26}H_{25}F_3N_4O_2S$ requires 514.

Example 74 and Example 75: (RS)-1-[2-(6,7-Difluoro-1-methyl-1*H*-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluorophenyl)-2-methyl-thiazol-4-yl]-methanone and (RS)-1-[2-(4,5-Difluoro-1-methyl-1*H*-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluorophenyl)-2-methyl-thiazol-4-yl]-methanone
(RS)-1-[2-(4,5-Difluoro-1*H*-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone, E36 (400mg, 0.85mmol) was added slowly to an ice-cooled

slurry of sodium hydride (68mg, 1.7mmol, 60% dispersion in mineral oil) in DMF (10ml). After stirring for a further 0.5h, iodomethane (266mg, 0.87mmol) was added. The mixture was stirred at room temperature for 72h then partitioned between water and ethyl acetate. The organic phase was washed with water, brine, dried (Na_2SO_4) and the solvent removed *in vacuo*. Purification by HPLC (Supercosil ABZ$^+$, 5-95% acetonitrile containing 0.1% trifluoroacetic acid-water containing 0.1% trifluoroacetic acid) afforded the title compounds (structures assignment based on nOe experiments):

1-[2-(6,7-Difluoro-1-methyl-1*H*-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluorophenyl)-2-methyl-thiazol-4-yl]-methanone (76mg)

Mass spectrum (Electrospray LC/MS): Found 485 (MH^+). $C_{25}H_{23}F_3N_4OS$ requires 484.

^{1}H NMR δ: 0.75-1.85 (6H, bm), 2.42 and 2.72 (3H, s), 0.85-3.15 (2H, bm), 3.30 (1H, m), 3.42 (0.7H, m), 3.70 and 4.15 (3H, s), 4.25 (0.3H, m), 4.75 (0.3H, m), 5.10 (0.7H, m), 7.00 (3H, m), 7.35 (3H, m).

1-[2-(4,5-Difluoro-1-methyl-1*H*-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluorophenyl)-2-methyl-thiazol-4-yl]-methanone (106mg)

Mass spectrum (Electrospray LC/MS): Found 485 (MH^+). $C_{25}H_{23}F_3N_4OS$ requires 484.

^{1}H NMR δ: 0.75-1.90 (6H, bm), 2.25 and 2.70 (3H, s), 2.9-3.2 (2H, bm), 3.15-3.45 (1.7H, bm), 3.56 and 3.94 (3H, s), 4.25 (0.3H, m), 4.76 (0.3H, m), 5.09 (0.7H, m), 6.98 (3H, m), 7.08(1H, m), 7.36 (2H, m).

Example 76: (RS)-2-(1-{1-[5-(4-Fluorophenyl)-2-methyl-thiazol-4-yl]-methanoyl}-piperidin-2-ylmethyl)-benzofuran-3-carboxylic acid amide

To a solution of (RS)-2-(1-(2,2,2-trifluoro-ethanoyl)-piperidin-2-yl-methyl)-benzofuran-3-carbonitrile, D42 (480mg, 1.4mmol) in methanol (15ml) and water (3ml) was added potassium carbonate (700mg, 4.9mmol) and the mixture heated at reflux for 1.25h. The solvent was removed in vacuo and the residue was partitioned between dichloromethane and water and basified to pH14. The aqueous phase was re-extracted with dichloromethane (3X) . The combined organics were dried (Na_2SO_4) and the solvent removed *in vacuo* to afford a solid (0.34g, 99%). To a portion of this material (67mg, 0.28mmol) in dichloromethane was added 5-(4-fluorophenyl)-2-methyl-thiazole-4-carboxylic acid (73mg, 0.30mmol), EDC.HCl (60mg, 0.30mml) and 1-hydroxybenzotriazole (10mg). After 16h at room temperature the reaction mixture was washed with saturated aqueous sodium hydrogen carbonate and the organic phase applied directly onto a pre-packed silica gel column. Elution with ethyl acetate- methanol mixtures afforded the title compound as an amorphous solid (8mg, 6%).

Mass spectrum (Electrospray LC/MS): Found 478 (MH^+). $C_{26}H_{24}FN_3O_3S$ requires 477.

Example 77: (RS)-2-(1-{1-[4-(4-Fluorophenyl)-1-methyl-1*H*-pyrazol-3-yl]-methanoyl}-piperidin-2-ylmethyl)-benzofuran-3-carboxylic acid amide

The title compound (7mg, 5%), was prepared as described for E76 from (RS)-2-(1-(2,2,2-trifluoro-ethanoyl)-piperidin-2-yl-methyl)-benzofuran-3-carbonitrile, D42 and 4-(4-fluorophenyl)-1-methyl-1H-pyrazole carboxylic acid (61mg, 0.3mmol)

Mass spectrum (Electrospray LC/MS): Found 461 (MH^+). $C_{26}H_{25}FN_4O_3$ requires 460.

Example 78: (RS)-1-[3-(4,5-Difluoro-1*H*-benzoimidazol-2-ylmethyl)-morpholin-4-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone

The title compound (93mg, 36%) was prepared from (4-{1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-morpholin-3-yl)-acetic acid, D45 according to the procedure described for Example 27.

Mass spectrum (Electrospray LC/MS): Found 473 (MH^+). $C_{23}H_{19}F_3N_4O_2S$ requires 472.

Example 79:(RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-(2-furo[3,2-b]-pyridin-2-ylmethyl-piperidin-1-yl)methanone

The title compound was prepared using the method of Example 4, from 5-(4-fluoro-phenyl)-2-methyl-thiazole-4-carboxylic acid (120mg, 0.5mmol) and (RS)-2-piperidin-2-ylmethyl-furo[3,2-b]pyridine, D47 (108mg, 0.5mmol), as a colourless solid (95mg, 43%).

Mass spectrum (Electrospray LC/MS): Found 436 (MH^+). $C_{24}H_{22}FN_3O_2S$ requires 435.

Example 80:(RS)-1-[4-(4-Fluoro-phenyl)-1-methyl-1H-pyrazole-3-yl)-(2-furo[3,2-b]pyridin-2-ylmethyl-piperidin-1-yl)methanone

The title compound was prepared using the method of Example 4, from 4-(4-fluoro-phenyl)-1-methyl-1H-pyrazole-3-carboxylic acid (110mg, 0.5mmol) and (RS)-2-Piperidin-2-ylmethyl-furo[3,2-b]pyridine, D47(108mg, 0.5mmol), as a colourless solid (130mg, 62%).

Mass spectrum (Electrospray LC/MS): Found 419 (MH^+). $C_{24}H_{23}FN_4O_2$ requires 418.

Example 81: (RS)-1-[2-(3-Bromo-benzofuran-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone

To (RS)-2-(2-benzofuranylmethyl)-1-((5-(4-fluorophenyl)-2-methyl-thiazol-4-yl)-carbonyl)-piperidine, E1 (0.90g, 2mmol) in dry diethyl ether (10ml) and dichloromethane (20ml) cooled to -12°C under argon, was added drop-wise a solution of bromine (0.36g, 2mmol) in dichloromethane (10ml) over 0.5h. The resulting solution was warmed to ambient temperature over 1.5h, then stirred for a further 18h. The reaction mixture was evaporated then re-evaporated from dichloromethane (3X). The resulting amorphous solid was chromatographed (silica gel with ethyl acetate-hexane mixtures) to afford the title compound as an amorphous solid (0.27g, 25%).

Mass spectrum (Electrospray LC/MS) Found 513 (MH^+). $C_{25}H_{22}{}^{79}BrFN_2O_2S$ requires 512.

Example 82: (RS)-2-(1-{1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-piperidin-2-ylmethyl)-benzofuran-3-carbonitrile

To (RS)-1-[2-(3-bromo-benzofuran-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone, E81 (270mg, 0.53mmol) in N-methyl-pyrrolidinone (8ml) was added copper(I)cyanide (96mg, 1.06mmol) and the mixture stirred under argon at reflux for 6h. The reaction mixture was cooled, poured into water (80ml) and ethyl acetate (50ml) and then filtered through kieselguhr. The filtrate was separated and the aqueous phase extracted with ethyl acetate (2X). The combined organics were washed with water (4X50ml), dried and the solvent removed *in vacuo* . Chromatography (silica gel) afforded the title compound as a white amorphous solid (94mg, 39%).

Mass spectrum (Electrospray LC/MS) Found 460 (MH^+). $C_{26}H_{22}FN_3O_2S$ requires 459.

Example 83: (RS)- 1-[2-(5-Fluorobenzofuran-2-ylmethyl)-4-methylpiperazin-1-yl]-1-[5-(4-fluorophenyl)-2-methythiazol-4-yl]methanone.hydrochloride

The title compound was prepared from (RS)-3-(5-fluorobenzofuran-2-ylmethyl)-1-methylpiperazine, D51 using the method of Example 1.

Mass spectrum (Electrospray LC/MS): Found 468 (MH^+). $C_{25}H_{23}F_2O_2S$ requires 467.

Example 84: (RS)-1-(2-Benzofuran-2-ylmethyl-4-methyl-piperazin-1-yl)-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl)]-methanone

The title compound (0.53g, 32%) was obtained from (RS)-3-benzofuran-2-ylmethyl-1-methyl-piperazine, D56 (0.89g, 3.8mmol) using the method of Example 1.

Mass spectrum (Electrospray LC/MS): Found 450 (MH^+). $C_{25}H_{24}FN_3O_2S$ requires 449.

Example 85: (RS)-1-(2-Benzofuran-2-ylmethyl-piperazin-1-yl)-1-[5-(4-fluorophenyl)-2-methyl-thiazol-4-yl]-methanone.hydrochloride

To (RS)-1-(2-benzofuran-2-ylmethyl-4-methyl-piperazin-1-yl)-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl)]-methanone, E84 (0.45g, 1mmol) in 1,2-dichloroethane (10ml) under argon at 0°C was added *N,N*-diisopropylethylamine(0.52 ml, 3mmol) followed by dropwise addition of 1-chloroethylchloroformate (0.77 ml, 6mmol) over 1-2 min. After 5 min, the reaction mixture was warmed to ambient temperature over 0.5h, and then heated at 65°C for 4.5h. Additional *N,N*-diisopropylethylamine (0.52ml, 3mmol) was added and heating continued for a further 2h. The reaction was cooled and evaporated, and the residue refluxed in methanol (25 ml) for 2.5h. The cooled reaction was evaporated and partitioned between dichloromethane (50 ml) and saturated aqueous sodium bicarbonate (25ml), aqueous phase extracted with dichloromethane (2 x 25ml). The combined organic extracts were dried (Na_2SO_4), evaporated and the residue chromatographed on silica gel eluting with methanol ethyl acetate mixtures to afford the free-base of the title compound (0.23g, 52%). A sample was converted to the hydrochloride salt by dissolving in methanol/dichloromethane and treating with excess 1M HCl in diethyl ether. Removal of the solvent *in vacuo* afforded the title compound as an amorphous solid.

Mass spectrum (Electrospray LC/MS): Found 458 (MNa^+). $C_{24}H_{22}FN_3O_2S$ requires 435.

Example 86: 1-{(RS)-2-[(RS)-1-(5-Fluoro-benzofurany-2-yl)-1-hydroxy-methyl]-4-methyl-piperazin-1-yl}-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone

The title compound (0.043g, 59%) was obtained from (RS)-1-(5-fluoro-benzofuran-2-yl)-1-((RS)-4-methyl-piperazin-2-yl)-methanol, D57 and 5-(4-(fluorophenyl)-2-methyl-thiazole-4-carbonyl chloride (0.043g, 0.16mmol) using the method of Example 1.

Mass spectrum (Electrospray LC/MS): Found 506 (MNa^+). $C_{25}H_{23}F_2N_3O_3S$ requires 483.

Example 87: 1-{(RS)-2-[(RS)-1-(5-Fluoro-benzofurany-2-yl)-1-hydroxy-methyl]-4-methyl-piperazin-1-yl}-1-(2-trifluoromethoxy-phenyl)-methanone

The title compound (0.034g, 50%) was obtained from (RS)-1-(5-fluoro-benzofuran-2-yl)-1-((RS)-4-methyl-piperizan-2-yl)-methanol, D57 and 2-(trifluoromethoxy)benzoyl chloride using the method of Example 1.

Mass spectrum (Electrospray LC/MS): Found 453 (MH^+). $C_{22}H_{20}F_4N_2O_4$ requires 452.

Example 88: (RS)-1-[2-(1-{1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-piperidin-2-ylmethyl)-benzofuran-3-yl]-ethanone

The title compound (120mg, 41%) was obtained from (RS)-1-[2-(3-bromo-benzofuran-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone, E81 (320mg, 0.62mmol) using the method of Example 68.

Mass spectrum (Electrospray LC/MS): Found 477 (MH^+). $C_{27}H_{25}FN_2O_3S$ requires 476.

Example 89a and Example 89b: (R)-1-[2-(5,6-Difluoro-1*H*-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone and(S)-1-[2-(5,6-Difluoro-1*H*-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone

(RS)-1-[2-(5,6-Difluoro-1*H*-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone E35 (380 mg) was separated to give the title compounds (stereochemistry not assigned) on a Chiralpak AD column (250mm x 19mm i.d.; 10 micron particle size); Mobile Phase: n-hexane, HiPerSiolv:ethanol, 99.7%v/v-100%v/v, Analar: triethylamine, Analar (90:10:0.25 v/v/v): pre-mixed: isocratic procedure; injecting at 2.5ml at concentation of 20mg/ml racemate in ethanol, 99.7%v/v-100%v/v, Analar.

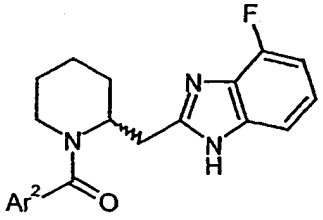
Faster eluting enantiomer (132mg, >99.8% e.e.):

Mass spectrum (Electrospray LC/MS): Found 471 (MH^+). $C_{24}H_{21}F_3N_4OS$ requires 470

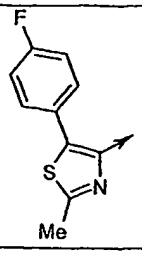
Slower eluting enantiomer (173mg, >99.8%e.e.):

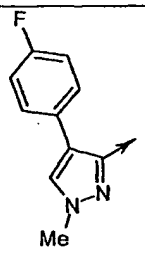
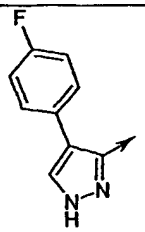
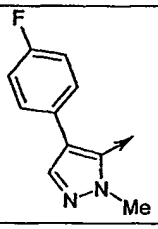
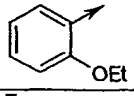
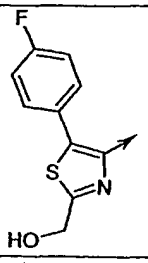
Mass spectrum (Electrospray LC/MS): Found 471 (MH^+). $C_{24}H_{21}F_3N_4OS$ requires 470

Table 5



The compounds of Examples 113-118 were prepared from the appropriate carboxylic acid and (RS)-4-fluoro-2-piperidin-2-ylmethyl-1H-benzoimidazole, D58 using a procedure similar to that described in Example 2 or Example 4.

Example	Ar^2	Method	Mass Spectrum (Electrospray LC/MS)
113		E2	Found MH^+ 453. $C_{24}H_{22}F_2N_4OS$ requires 452.

114		E2	Found MH^+ 436. $C_{24}H_{23}F_2N_5O$ requires 435.
115		E2	Found MH^+ 422. $C_{23}H_{21}F_2N_5O$ requires 421.
116		E2	Found MH^+ 436. $C_{24}H_{23}F_2N_5O$ requires 435.
117		E2	Found MH^+ 382. $C_{22}H_{24}FN_3O_2$ requires 381.
118		E4	Found M-1 467. $C_{24}H_{22}F_2N_4O_2S$ requires 468. (API LC/MS)

Example 119: (RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-{2-[4-(1-hydroxy-ethyl)-1*H*-benzoimidazol-2-ylmethyl]-piperidin-1-yl}-methanone

Sodium borohydride (145mg) was added portionwise over 2 min. to a cooled (0-10°C) solution of (RS)-1-[2-(4-acetyl-1*H*-benzimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluorophenyl)-2-methylthiazol-4-yl]methanone, E68 (365mg) in methanol (10ml). After stirring for a further 2.5h at room temperature, water (100ml) was added and the mixture was extracted with dichloromethane (2X). The combined organics were dried (Na_2SO_4), evaporated and the residue chromatographed (silica gel, 0-100% ethyl acetate-hexane then 2-10% methanol-ethyl acetate) to afford the title compound as a solid (320mg).

Mass spectrum (Electrospray LC/MS): Found 479 (MH^+). $C_{26}H_{27}FN_4O_2S$ requires 478.

Example 120: (RS)- 1-(2-Benzofuran-2-ylmethyl-piperidin-1-yl)-1-[5-(4-chloro-phenyl)-2-methyl-thiazol-4-yl]-methanone

The title compound (100mg) was prepared from (RS)-2-(2-benzofuranylmethyl)piperidine, D3 (64mg) and 5-(4-chloro-phenyl)-2-methyl-thiazole-4-carboxylic acid (76mg) by a procedure similar to that described for Example 2.
Mass spectrum (API LC/MS): Found 451 (MH^+). $C_{25}H_{23}{}^{35}ClN_2O_2S$ requires 450.

Example 121: (RS)- 1-[2-(3-Chloro-furo[3,2-b]pyridin-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
A solution of chlorine (28mg) in dichloromethane (3ml) was added to a cooled (-12°C) solution (RS)-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-(2-furo[3,2-b]-pyridin-2-ylmethyl-piperidin-1-yl)methanone, E79 (170mg) in dichloromethane (4ml). After stirring at -12°C for 0.5h the reaction mixture was stirred at room temperature for 16h then the solution was washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4) and the solvent removed *in vacuo*. Chromatography (silica gel, 0-100% ethyl acetate-hexane then 0-10% methanol-ethyl acetate) afforded the title compound (24mg).
Mass spectrum (Electrospray LC/MS): Found 470 (MH^+). $C_{24}H_{21}{}^{35}ClFN_3O_2S$ requires 469.

Example 122: (RS)-1-[2-(5,6-Difluoro-1-methyl-1H-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-hydroxymethyl-thiazol-4-yl]-methanone
The title compound (15mg) was prepared from 5-(4-fluoro-phenyl)-2-hydroxymethyl-thiazole-4-carboxylic acid (84mg) and (RS)-5,6-difluoro-1-methyl-2-piperidin-2-ylmethyl-1H-benzoimidazole, D61 (86mg) by a procedure similar to that described for Example 4.
Mass spectrum (Electrospray LC/MS): Found 501(MH^+). $C_{25}H_{23}F_3N_4O_2S$ requires 500.

Example 123: (RS)-1-[2-(5-Chloro-benzofuran-2-ylmethyl)-4-methyl-piperazin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
The title compound (135mg) was prepared from 5-(4-fluoro-phenyl)-2-methyl-thiazole-4-carbonyl chloride (211mg) and 3-(5-Chloro-benzofuran-2-ylmethyl)-1-methyl-piperazine, D63 (200mg) by a procedure similar to that described for Example 1.
Mass spectrum (API^+ LC/MS): Found 484(MH^+). $C_{25}H_{23}{}^{35}ClFN_3O_2S$ requires 483

Example 124: (RS)-1-[2-(5-Chloro-benzofuran-2-ylmethyl)-piperazin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]- methanone
The title compound was prepared from 1-[2-(5-chloro-benzofuran-2-ylmethyl)-4-methyl-piperazin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone, E123 (95mg) by a procedure similar to that described for Example 85.
Purification by HPLC (Supercosil ABZ^+, 5-95% acetonitrile containing 0.1% trifluoroacetic acid-water containing 0.1% trifluoroacetic acid) afforded the title compound (5mg) as the TFA salt.
Mass spectrum (Electrospray LC/MS): Found 470(MH^+). $C_{24}H_{21}{}^{35}ClFN_3O_2S$ requires 469.

Example 125: (RS)-1-[2-(5,7-Dichloro-benzofuran-2-ylmethyl)-4-methyl-piperazin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
The title compound (80mg) was prepared from 5-(4-fluoro-phenyl)-2-methyl-thiazole-4-carbonyl chloride (498mg) and (RS)-3-(5,7-dichloro-benzofuran-2-ylmethyl)-1-methyl-piperazine, D65 (530mg) by a procedure similar to that described for Example 1.

Mass spectrum (API$^+$ LC/MS): Found 518(MH^+). $C_{25}H_{22}{}^{35}Cl_2FN_3O_2S$ requires 517.

Example 126: (RS)-1-[2-(5,7-Dichloro-benzofuran-2-ylmethyl)-piperazin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4- yl]-methanone

The title compound was prepared from (RS)-1-[2-(5,7-dichloro-benzofuran-2-ylmethyl)-4-methyl-piperazin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone E125 (72mg) by a procedure similar to that described for Example 85. Purification by HPLC (Supercosil ABZ$^+$, 5-95% acetonitrile containing 0.1% trifluoroacetic acid-water containing 0.1% trifluoroacetic acid) afforded the title compound (6mg) as the TFA salt.

Mass spectrum (Electrospray LC/MS): Found 504(MH^+). $C_{24}H_{20}{}^{35}Cl_2FN_3O_2S$ requires 503.

Example 127: (RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[2-(1H-indol-2-ylmethyl)-piperidin-1-yl]-methanone

(RS)- 1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-{2-[1-(2-trimethylsilanyl-ethoxymethyl)-1H-indol-2ylmethyl]-piperidin-1-yl}-methanone (130mg) was prepared from (RS)- 2-piperidin-2-ylmethyl-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-indole, D68 (520mg) and 5-(4-fluoro-phenyl)-2-methyl-thiazole-4-carbonyl chloride (512mg) according to a procedure similar to that for Example 1. A stirring solution of the above amide (125mg) in dry THF (5ml) was treated with a solution of tetrabutylammonium fluoride (2.2mmol) in THF (5ml). Once tlc indicated the reaction had gone to completion, the reaction mixture was poured into water and the product extracted with ethyl acetate. The combined organics were washed with brine, dried (Na_2SO_4) and the solvent removed *in vacuo*. Chromatography (silica gel, 0-100% pentane-ethyl acetate followed by preparative tlc, 40% ethyl acetate-pentane) afforded the title compound as a white solid (2.5mg).

Mass spectrum (Electrospray LC/MS): Found 434(MH^+). $C_{25}H_{24}FN_3OS$ requires 433.

Example 128: (RS)- 5-[1-(2-Benzofuran-2-ylmethyl-piperidin-1-yl)-methanoyl]-4*H*-benzo[1,4]oxazin-3-one

The title compound (65mg) was prepared from (RS)-2-(2-benzofuranylmethyl)piperidine, D3 (65mg) and 3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine-5-carboxylic acid (39mg) by a procedure similar to that for Example 2.

Mass spectrum (Electrospray LC/MS): Found 391(MH^+). $C_{23}H_{22}N_2O_4$ requires 390.

Example 129: (RS)- 1-[2-(5-Bromo-benzofuran-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone

The title compound (490mg) was prepared from 5-(4-fluoro-phenyl)-2-methyl-thiazole-4-carbonyl chloride (488mg) and (RS)-2-(5-bromo-benzofuran-2-ylmethyl)-piperidine, D70 (530mg) by a procedure similar to that described for Example 1.

Mass spectrum (Electrospray LC/MS): Found 513 (MH^+). $C_{25}H_{22}{}^{79}BrFN_2O_2S$ requires 512.

Example 130: (RS)- 1-[2-(5-Cyano-benzofuran-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone

The title compound (19mg) was prepared from (RS)- 1-[2-(5-bromo-benzofuran-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone, E129 (420mg) and copper(I)cyanide according to a procedure similar to that described for Example 67.
Mass spectrum (API$^+$ LC/MS): Found 460 (MH^+). $C_{26}H_{22}FN_3O_2S$ requires 459.

Example 131: (RS)- 1-[2-(4-Bromo-benzofuran-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
The title compound (0.45g) was prepared from 5-(4-fluoro-phenyl)-2-methyl-thiazole-4-carbonyl chloride (0.89g) and 2-(4-bromo-benzofuran-2-ylmethyl)-piperidine, D72 (0.88g) by a procedure similar to that described for Example 1.
Mass spectrum (Electrospray LC/MS): Found 513 (MH^+). $C_{25}H_{22}{}^{79}BrFN_2O_2S$ requires 512.

Example 132:(RS)- 1-[2-(4-Cyano-benzofuran-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
The title compound (80mg) was prepared from (RS)- 1-[2-(4-bromo-benzofuran-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone, E131 (400mg) and copper(I)cyanide according to a procedure similar to that described for Example 67.
Mass spectrum (Electrospray LC/MS): Found 460 (MH^+). $C_{26}H_{22}FN_3O_2S$ requires 459.

Example 133: (RS) -1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[2-(3-methyl-benzofuran-2-ylmethyl)-piperidin-1-yl]-methanone
The title compound (18mg) was prepared from (RS)-2-(3-methyl-benzofuran-2-ylmethyl)-piperidine, D74 (92mg) and 5-(4-fluoro-phenyl)-2-methyl-thiazole-4-carboxylic acid (190mg) according to a procedure similar to that described for Example 4.
Mass spectrum (API LC/MS): Found 449 (MH^+). $C_{26}H_{25}FN_2O_2S$ requires 448.

Example 134: (RS)- 1-[2-(4-Fluoro-benzofuran-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
The title compound (60mg) was prepared from (RS)-2-(4-fluoro-benzofuran-2-ylmethyl)-piperidine, D76 (157mg) and 5-(4-fluoro-phenyl)-2-methyl-thiazole-4-carboxylic acid (160mg) according to a procedure similar to that described for Example 4.
Mass spectrum (API LC/MS): Found 453 (MH^+). $C_{25}H_{22}F_2N_2O_2S$ requires 452.

Example 135: (RS)- 1-[2-(4-Fluoro-benzofuran-2-ylmethyl)-piperidin-1-yl]-1-[4-(4-fluoro-phenyl)-1-methyl-1H- pyrazol-3 -yl]-methanone
The title compound (45mg) was prepared from (RS)-2-(4-fluoro-benzofuran-2-ylmethyl)-piperidine, D76 (157mg) and 4-(4-fluoro-phenyl)-1-methyl-1*H*- pyrazole-3-carboxylic acid (160mg) according to a procedure similar to that described for Example 4.
Mass spectrum (API LC/MS): Found 436 (MH^+). $C_{25}H_{23}F_2N_3O_2$ requires 435.

Example 136: (RS)- 1-[2-(4,6-Dichloro-benzofuran-2-ylmethyl)-4-methyl-piperazin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone

The title compound (107mg) was prepared from 5-(4-fluoro-phenyl)-2-methyl-thiazole-4-carbonyl chloride (241mg) and 3-(4,6-dichloro-benzofuran-2-ylmethyl)-1-methyl-piperazine, D78 (263mg) by a procedure similar to that described for Example 1.
Mass spectrum (Electrospray LC/MS): Found 518 (MH^+). $C_{25}H_{22}{}^{35}Cl_2FN_3O_2S$ requires 517.

Example 137 (RS)- 1-[2-(4,6-Dichloro-benzofuran-2-ylmethyl)-piperazin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4- yl]-methanone
The title compound was prepared from (RS)- 1-[2-(4,6-dichloro-benzofuran-2-ylmethyl)-4-methyl-piperazin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone, E136 (87mg) by a procedure similar to that described for Example 85.
Purification by HPLC (Supercosil ABZ$^+$, 5-95% acetonitrile containing 0.1% trifluoroacetic acid-water containing 0.1% trifluoroacetic acid) afforded the title compound (mg) as the TFA salt.
Mass spectrum (Electrospray LC/MS): Found 504(MH^+). $C_{24}H_{20}{}^{35}Cl_2FN_3O_2S$ requires 503.

Example 138: (RS)- 1-(2-Benzofuran-2-ylmethyl-pyrrolidin-1-yl)-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
The title compound (45mg) was prepared from (RS)- 2-benzofuran-2-ylmethyl-pyrrolidine D81 (114mg) and 5-(4-fluoro-phenyl)-2-methyl-thiazole-4-carboxylic acid (147mg) according to a procedure similar to that described for Example 4.
Mass spectrum (Electrospray LC/MS): Found 421 (MH^+). $C_{24}H_{21}FN_2O_2S$ requires 420.

Example 139: (RS)- 1-(2-Benzofuran-2-ylmethyl-pyrrolidin-1-yl)-1-[4-(4-fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanone
The title compound (29mg) was prepared from (RS)- 2-benzofuran-2-ylmethyl-pyrrolidine D81 (114mg) and 4-(4-fluoro-phenyl)-1-methyl-1*H*- pyrazole-3-carboxylic acid (137mg) according to a procedure similar to that described for Example 4.
Mass spectrum (Electrospray LC/MS): Found 404 (MH^+). $C_{24}H_{22}FN_3O_2$ requires 403.

Example 140: (RS)- 1-(2-Benzo[b] thiophen-2-ylmethyl-piperidin-1-yl)-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
The title compound (40mg) was prepared from 2-benzo[b]thiophen-2-ylmethyl-piperidine D83(133mg) and 5-(4-fluoro-phenyl)-2-methyl-thiazole-4-carboxylic acid (136mg) according to a procedure similar to that described for Example 4.
Mass spectrum (Electrospray LC/MS): Found 451 (MH^+). $C_{25}H_{23}FN_2OS_2$ requires 450.

Example 141: (RS)- 1-(2-Benzo[b]thiophen-2-ylmethyl-piperidin-1-yl)-1-[4-(4-fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanone
The title compound (6mg) was prepared from 2-benzo[b]thiophen-2-ylmethyl-piperidine D83(133mg) and 4-(4-fluoro-phenyl)-1-methyl-1*H*- pyrazole-3-carboxylic acid (140mg) according to a procedure similar to that described for Example 4.
Mass spectrum (Electrospray LC/MS): Found 434 (MH^+). $C_{25}H_{24}FN_3OS$ requires 433.

Example 142: (RS)- 1-(2-Benzo[b]thiophen-2-ylmethyl-piperidin-1-yl)-1-quinolin-8-yl-methanone

The title compound (4mg) was prepared from 2-benzo[b]thiophen-2-ylmethyl-piperidine D83(133mg) and 8-quinoline carboxylic acid (109mg) according to a procedure similar to that described for Example 4.
Mass spectrum (Electrospray LC/MS): Found 387 (MH^+). $C_{24}H_{22}N_2OS$ requires 386

Example 143: (RS)-1-(2-Benzofuran-2-ylmethyl-piperidin-1-yl)-1-(2-methyl-5-phenyl-thiazol-4-yl)-methanone
The title compound (90mg) was prepared from (RS)-2-(2-benzofuranylmethyl) piperidine, D3 (100mg) and 5-phenyl-2-methyl-thiazole-4-carbonyl chloride (122mg) according to a procedure similar to that for Example 1.
Mass spectrum (Electrospray LC/MS): Found 417 (MH^+). $C_{25}H_{24}N_2O_2S$ requires 416.

Example 144: 1-[(S)-2-(5,6-Difluoro-1*H*-benzoimidazol-2-ylmethyl)-pyrrolidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-hydroxymethyl-thiazol-4-yl]-methanone
The title compound (65mg) was prepared from 5,6-difluoro-2-(*S*)-1-pyrrolidin-2-ylmethyl-1*H*-benzoimidazole, D27(153mg) and 5-(4-fluoro-phenyl)-2-hydroxymethyl-thiazole-4-carboxylic acid (205mg) according to a procedure similar to that for Example 4.
Mass spectrum (Electrospray LC/MS): Found 473 (MH^+). $C_{23}H_{19}F_3N_4O_2S$ requires 472.

Example 145: (RS)- 1-(2-Benzofuran-2-ylmethyl-piperidin-1-yl)-1-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone
The title compound (33mg) was prepared from (RS)-2-(2-benzofuranylmethyl) piperidine, D3 (108mg) and 2-(3-methyl-[1,2,4]oxadiazol-5-yl)-benzoic acid (102mg) according to a procedure similar to that for Example 2.
Mass spectrum (Electrospray LC/MS): Found 402 (MH^+). $C_{24}H_{23}N_3O_3$ requires 401.

Example 146a and Example 146b: (R)-1-[2-(4,6-Difluoro-1*H*-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone and (S)-1-[2-(4,6-Difluoro-1*H*-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone (enantiomers of Example 32)(RS)-1-[2-(4,6-Difluoro-1*H*-benzoimidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone, E32 was separated to give the title compounds (stereochemistry not assigned) using the following procedures:
Analytical separation: 10uL of diluted sample (compound in methanol) was separated on a 4.6x250mm,10 micron, analytical ChiralCel OD column. A Berger Analytical SFC (Super Critical Fluid) instrument was used with system parameters as follows: mobile phase= 90% CO2: 10% organic modifier, organic modifier = 90%methanol:10% chloroform v/v, 3000psi, 2mL/min, 40C λ=254 nm
The enantiomers eluted at 6.4 min. and 8.1 min.
Preparative separation: Scale-up was preformed on a Prochrom Super C.20 instrument. The instrument parameters were as follows : 40C, 21 MPa, 40g/min CO2+ 4.5ml/min organic modifier (as above), λ=300nm, ChiralCel OD 20x250mm, 10 micron column. 30 mg of racemate was introduced per cycle. Sample concentration= 875mg/13ml solvent (sample solvent

= 5ml chloroform and 8mL methanol). Cycle time (run time)= 17minutes. The enantiomers eluted at 10.2 and 13.6 min. Elution times measured at peak maxima.

It is understood that the present invention covers all combinations of particular and preferred groups described herein above.

Determination of Orexin-1 Receptor Antagonist Activity

The orexin-1 receptor antagonist activity of the compounds of formula (I) was determined in accordance with the following experimental method.

Experimental Method

CHO-DG44 cells expressing the human orexin-1 receptor were grown in cell medium (MEM medium with Earl's salts) containing 2 mM L-Glutamine, 0.4 mg/mL G418 Sulphate from GIBCO BRL and 10% heat inactivated fetal calf serum from Gibco BRL. The cells were seeded at 20,000 cells/100 µl/well into 96-well black clear bottom sterile plates from Costar which had been pre-coated with 10 µg/well of poly-L-lysine from SIGMA. The seeded plates were incubated overnight at 37C in 5% CO_2.

Agonists were prepared as 1 mM stocks in water:DMSO (1:1). EC50 values (the concentration required to produce 50% maximal response) were estimated using 11x half log unit dilutions (Biomek 2000, Beckman) in Tyrode's buffer containing probenecid (10 mM HEPES with 145mM NaCl, 10mM glucose, 2.5 mM KCl, 1.5 mM $CaCl_2$, 1.2 mM $MgCl_2$ and 2.5mM probenecid; pH7.4). Antagonists were prepared as 10 mM stocks in DMSO (100%). Antagonist IC50 values (the concentration of compound needed to inhibit 50% of the agonist response) were determined against 3.0 nM human orexin-A using 11x half log unit dilutions in Tyrode's buffer containing 10% DMSO and probenecid.

On the day of assay 50 µl of cell medium containing probenecid (Sigma) and Fluo3AM (Texas Fluorescence Laboratories) was added (Quadra, Tomtec) to each well to give final concentrations of 2.5 mM and 4 µM, respectively. The 96-well plates were incubated for 60 min at 37C in 5% CO2. The loading solution containing dye was then aspirated and cells were washed with 4x150 µl Tyrode's buffer containing probenecid and 0.1% gelatin (Denley Cell Wash). The volume of buffer left in each well was 125 µl. Antagonist or buffer (25 µl) was added (Quadra) the cell plates gently shaken and incubated at 37C in 5% CO_2 for 30 minutes. Cell plates were then transferred to the Fluorescent Imaging Plate Reader (FLIPR, Molecular Devices) instrument. Prior to drug addition a single image of the cell plate was taken (signal test), to evaluate dye loading consistency. The run protocol used 60 images taken at 1 second intervals followed by a further 24 images at 5 second intervals. Agonists were added (by the FLIPR) after 20 seconds (during continuous reading). From each well, peak fluorescence was determined over the whole assay period and the mean of readings 1-19 inclusive was subtracted from this figure. The peak increase in fluorescence was plotted against compound concentration and iteratively curve fitted using a four parameter logistic fit (as described by Bowen and Jerman, *TiPS*, 1995, 16, 413-417) to generate a concentration effect value. Antagonist Kb values were calculated using the equation:

Kb= IC50/(1+([3/EC50])

where EC50 was the potency of human orexin-A determined in the assay (in nM terms) and IC50 is expressed in molar terms.

Compounds of Examples tested according to this method had pKb values >7.0 to 9.4 at the human cloned orexin-1 receptor.

The orexin-2 receptor antagonist activity of the compounds of formula (I) was determined in accordance with the following experimental method.

Experimental Method

CHO-DG44 cells expressing the human orexin-2 receptor were grown in cell medium (MEM medium with Earl's salts) containing 2 mM L-Glutamine, 0.4 mg/mL G418 Sulphate from GIBCO BRL and 10% heat inactivated fetal calf serum from Gibco BRL. The cells were seeded at 20,000 cells/100 µl/well into 96-well black clear bottom sterile plates from Costar which had been pre-coated with 10 µg/well of poly-L-lysine from SIGMA. The seeded plates were incubated overnight at 37C in 5% CO_2.

Agonists were prepared as 1 mM stocks in water:DMSO (1:1). EC50 values (the concentration required to produce 50% maximal response) were estimated using 11x half log unit dilutions (Biomek 2000, Beckman) in Tyrode's buffer containing probenecid (10 mM HEPES with 145mM NaCl, 10mM glucose, 2.5 mM KCl, 1.5 mM $CaCl_2$, 1.2 mM $MgCl_2$ and 2.5mM probenecid; pH7.4). Antagonists were prepared as 10 mM stocks in DMSO (100%). Antagonist IC50 values (the concentration of compound needed to inhibit 50% of the agonist response) were determined against 10.0 nM human orexin-A using 11x half log unit dilutions in Tyrode's buffer containing 10% DMSO and probenecid.

On the day of assay 50 µl of cell medium containing probenecid (Sigma) and Fluo3AM (Texas Fluorescence Laboratories) was added (Quadra, Tomtec) to each well to give final concentrations of 2.5 mM and 4 µM, respectively. The 96-well plates were incubated for 60 min at 37C in 5% CO_2. The loading solution containing dye was then aspirated and cells were washed with 4x150 µl Tyrode's buffer containing probenecid and 0.1% gelatin (Denley Cell Wash). The volume of buffer left in each well was 125 µl. Antagonist or buffer (25 µl) was added (Quadra) the cell plates gently shaken and incubated at 37C in 5% CO_2 for 30 min. Cell plates were then transferred to the Fluorescent Imaging Plate Reader (FLIPR, Molecular Devices) instrument. Prior to drug addition a single image of the cell plate was taken (signal test), to evaluate dye loading consistency. The run protocol used 60 images taken at 1 second intervals followed by a further 24 images at 5 second intervals. Agonists were added (by the FLIPR) after 20 sec (during continuous reading). From each well, peak fluorescence was determined over the whole assay period and the mean of readings 1-19 inclusive was subtracted from this figure. The peak increase in fluorescence was plotted against compound concentration and iteratively curve fitted using a four parameter logistic fit (as described by Bowen and Jerman, *TiPS*, 1995, 16, 413-417) to generate a concentration effect value. Antagonist Kb values were calculated using the equation:

Kb= IC50/(1+([3/EC50])

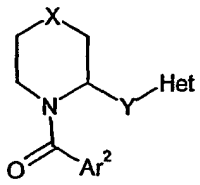
where EC50 was the potency of human orexin-A determined in the assay (in nM terms) and IC50 is expressed in molar terms.

Compounds of Examples tested according to this method had pKb values in the range 6.5 – 8.4 at the human cloned orexin-2 receptor.

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process, or use claims and may include, by way of example and without limitation the following claims:

CLAIMS

1. A compound of formula (I):



wherein

X represents a bond, oxygen, NR^3 or a group $(CH_2)_n$, wherein n represents 1, 2 or 3;

Y represents CH_2, CO, CH(OH), or $CH_2CH(OH)$;

Het is an optionally substituted bicyclic heteroaryl group containing up to 4 heteroatoms selected from N, O and S;

Ar^2 represents an optionally substituted phenyl or a 5- or 6-membered heterocyclyl group containing up to 3 heteroatoms selected from N, O and S, wherein the phenyl or heterocyclyl group is substituted by R^1 and further optional substituents; or Ar^2 represents an optionally substituted bicyclic aromatic or bicyclic heteroaromatic group containing up to 3 heteroatoms selected from N, O and S;

R^1 represents hydrogen, optionally substituted(C_{1-4})alkoxy, halo, cyano, optionally substituted(C_{1-6})alkyl, optionally substituted phenyl, or an optionally substituted 5- or 6-membered heterocyclyl group containing up to 4 heteroatoms selected from N, O and S;

R^3 represents hydrogen or an optionally substituent (C_{1-4})alkyl other than when Het is indolyl where R^3 represents hydrogen or (C_{1-4}) alkyl;

or a pharmaceutically acceptable salt thereof.

with the proviso that;

when X is NH, Y is CH_2 and Het is indolyl, Ar^2 is not 3,5-bis(trifluoromethyl)phenyl;

or the compound is not

(2R)-1-(3,5-dichlorobenzoyl)-2-[(1H-indol-3-yl)methyl]piperazine;

(2R)-2-[1H-indol-3-yl)methyl]-1-[3-methoxy-5-trifluoromethyl)benzoyl]piperazine;

1-benzolyl-2-[1H-indol-3-yl)methyl]piperazine.

2. A compound according to claim 1 wherein X is CH_2.

3. A compound according to claim 1 or 2 wherein Ar^2 represents optionally substituted phenyl, pyridinyl, thiazolyl, pyrazolyl, pyridazinyl, thienyl, naphthyl, triazolyl isoxazolyl, quinolinyl, or isoquinolinyl.

4. A compound according to any one of claims 1 to 3 wherein R^1 represents optionally substituted phenyl, pyridinyl, pyrazolyl pyrimidinyl or oxadiazolyl group.

5. A compound according to any one of claims 1 to 4 wherein Ar^2 is optionally substituted by C_{1-4})alkyl, hydroxy(C_{1-4})alkyl, R^aR^bN, (C_{1-4})alkoxy, $R^aR^bN(CH_2)n$, (C_{1-4})acyl, and (C_{1-4})alkylamido.

6. A compound according to any one of claims 1 to 5 wherein Het is benzimidazolyl, benzofuranyl or benzoxazolyl.

7. A compound according to any one of claims 1 to 6 wherein Y represents CH_2.

8. A compound of formula (I) as defined in any one of Examples 1 to 146, or a pharmaceutically acceptable salt of any one thereof.

9. A pharmaceutical composition comprising a compound of formula (I) as defined in any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

10. A method of treating or preventing diseases or disorders where an antagonist of a human orexin receptor is required, which comprises administering to a subject in need thereof an effective amount of a compound of formula (I) as defined in any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof.

11. A method of treating or preventing diseases or disorders where an antagonist of a human orexin receptor is required, which comprises administering to a subject in need thereof an effective amount of a compound selected from (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-ylmethyl)piperazine, (2R)-1-(3,5-dichlorobenzoyl)-2-[(1H-indol-3-yl)methyl]piperazine, (2R)-2-[1H-indol-3-yl)methyl]-1-[3-methoxy-5-trifluoromethyl)benzoyl]piperazine; or 1-benzolyl-2-[1H-indol-3-yl)methyl]piperazine.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/07009

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D417/14 C07D411/14 C07D407/14 C07D413/14 A61K31/445
A61P25/00 A61P3/04 A61P3/10 A61P15/00 C07D407/06
C07D491/04 C07D401/14 - C07D401/06 C07D409/14 C07D471/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 09024 A (JOHNS AMANDA ;PORTER RODERICK ALAN (GB); SMITHKLINE BEECHAM PLC (G) 25 February 1999 (1999-02-25) cited in the application claims 1,12 ---	1,10
A	WO 00 47576 A (JOHNS AMANDA ;PORTER RODERICK ALAN (GB); SMITHKLINE BEECHAM PLC (G) 17 August 2000 (2000-08-17) cited in the application claims 1,10 ---	1,10
A	WO 00 47580 A (COULTON STEVEN ;JOHNS AMANDA (GB); PORTER RODERICK ALAN (GB); SMIT) 17 August 2000 (2000-08-17) cited in the application claims 1,12 --- -/---	1,10

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 October 2002	18/11/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bakboord, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/07009

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 //(C07D417/14,307:00,277:00,211:00),(C07D417/14,307:00,263:00, 211:00),(C07D413/14,271:00,263:00,211:00),(C07D407/14,307:00, 231:00,211:00),(C07D417/14,307:00,277:00,213:00,211:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 01 96302 A (BRANCH CLIVE LESLIE ;JOHNSON CHRISTOPHER NORBERT (GB); THEWLIS KEV) 20 December 2001 (2001-12-20) claims 1,9	1,10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 October 2002	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bakboord, J

Form PCT/ISA/210 (second sheet) (July 1992)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1, 3-10 (all part), 11

Present claims 1, 3-10 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds for which X is CH2.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 02/07009

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 10 and 11 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound.

2. [X] Claims Nos.: - 1, 3-10 (all part), 11
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 02/07009

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
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			CA	2300178 A1	25-02-1999
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			WO	9909024 A1	25-02-1999
			JP	2001515075 T	18-09-2001
			US	6410529 B1	25-06-2002
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WO 0047580	A	17-08-2000	AU	2910600 A	29-08-2000
			WO	0047580 A2	17-08-2000
			EP	1144409 A2	17-10-2001
WO 0196302	A	20-12-2001	AU	7247601 A	24-12-2001
			WO	0196302 A1	20-12-2001